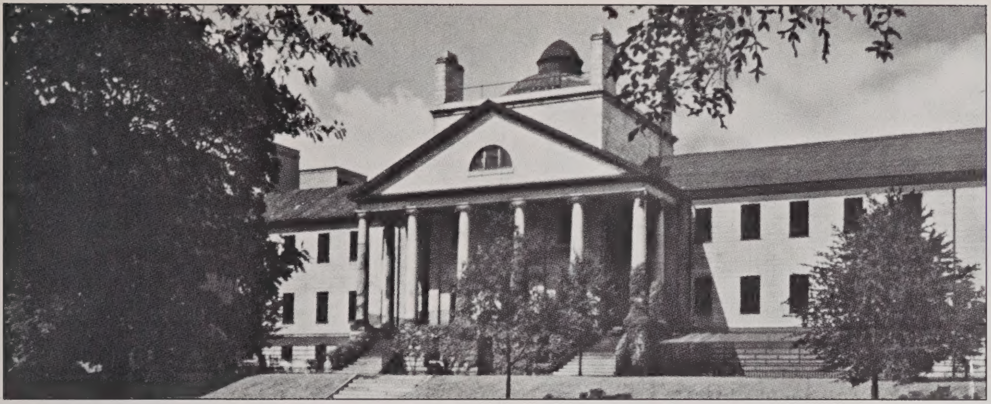

MGH
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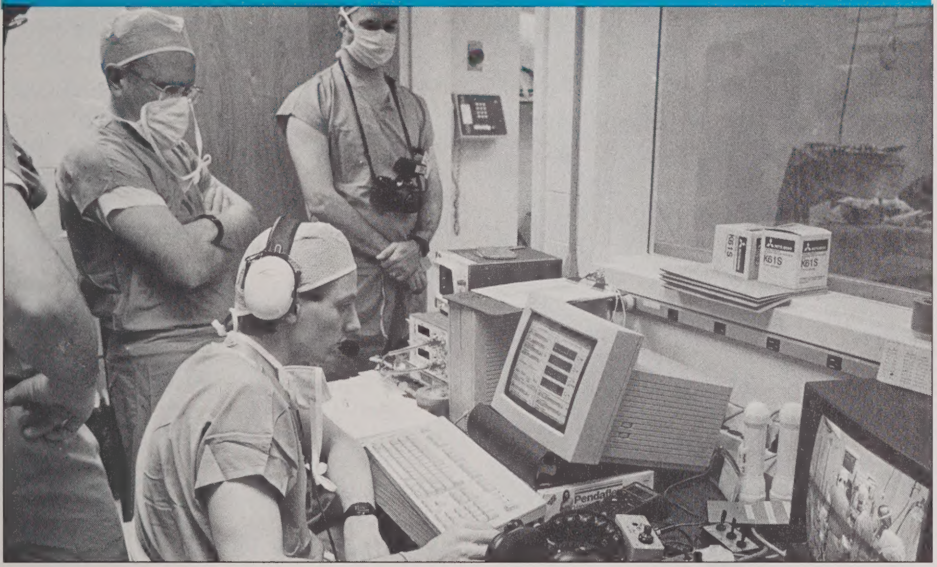
# New Training Tool May Add to Anesthesia Safety



*Daniel Burkhardt (seated), a Harvard medical student working with MGH staff on the simulator project, operates a computer to control readings that appear on anesthesia monitors. He is wearing a headset to receive directions from an instructor stationed in the operating room, which can be seen on the monitor in the far right. Behind him stand MGH anesthesiologist Stephen Small, MD, and David Gaba, MD, of Stanford.*

*THE OPERATION had just begun, when suddenly an alarm began to sound on the elaborate machine located at the head of the operating table. The anesthesiologist immediately checked the patient and the array of lights and numbers that reflect the patient's vital signs and the precise mixture of oxygen and anesthetic gases being delivered.*

*The supply of oxygen normally piped into the operating room had stopped. The anesthesiologist opened the emergency oxygen tank on the anesthesia machine, but it was empty. A technician sent to search for another tank came back to report that the key to the storage room was missing . . . .*

It seems like a medical example of Murphy's Law, but the scene — and others like it — was actually repeated several times last fall at a Boston teaching hospital. But it was no case of carelessness or coincidence, and no patient was in danger.

Instead it was a tryout of a new tool that may someday be incorporated into training those responsible for administering anesthesia and for helping ensure a patient's safety during a surgical procedure.

In a three-month pilot project, anesthetists from the MGH and four other Harvard teaching hospitals were testing a state-of-the-art anesthesia simulator — a machine that realistically recreates the experience of delivering anesthesia in an operating room. Like the simulators used by airline pilots, it allows anesthetists to

*(Continued on Page 4)*

## *In the Best Interest of the Child*

IT IS LESS and less unusual today for children to become involved with the legal system. From disputes over custody, to allegations of child abuse, to violent crimes committed by young people — court cases involving children are the stuff of newspaper headlines and the evening news.

But whether such cases are conducted under full media scrutiny or in relative privacy, they share many common themes. Who is best qualified to care for a child? Should an abusive parent be denied all access to a child? How can we prevent a

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## EDITORIAL

# A New But Old Need

IT STARTED WITH one young physician wanting to prepare to care for both adults and children. It became reality when the MGH Medical Service and the Children's Service created the opportunity. Over the last three years the program has rooted and developed limbs to support seven residents in training. And the number of participants will enlarge next year, reaching 10.

The page 7 article which chronicles the creation demonstrates an unusual quality one might not anticipate in a hospital with more than 1,000 inpatient beds, 10,000 employees, a broad scope of activities, and an often hectic pace. It can listen to the voice of a single intern, really listen. In this case, the Chiefs of Medicine and the Children's Service and the hospital administration reached the conclusion that the young doctor was correct. The United States of America — particularly the East and West Coasts — have failed miserably to train physicians who can treat an entire family from cradle to grave, the way doctors used to. And like virtually all the other hospitals, the MGH was not doing anything about the situation.

It is understandable why the Midwest has been a haven for training family doctors. In the Northeast distances to population centers with large numbers of physicians for every need are relatively small. Not so through much of the Midwest. For this and other reasons, teaching hospitals in geographically large states and regions have perhaps faced both greater need and demand to train family doctors.

It is painfully obvious that 10 MGH trainees will not dent the dearth of family doctors in even New England. But it is a not insignificant start. For if a private teaching hospital noted for producing internationally outstanding specialists can also dedicate itself to a new but old need, who knows what miracles a cluster of other private hospitals might perform. ■

## — Children

*(Continued from Page 1)*

delinquent child from becoming a criminal adult?

Judges and lawyers are experts in the intricacies of the legal system, but few have specialized knowledge regarding the psychology and development of children. Mental health professionals who care for children may not have the understanding of the law required to negotiate the confusing maze of the courts.

The Children and the Law Program, which recently became a division of the MGH Law and Psychiatry Service, specializes in bringing together the legal and child development perspectives to find the best solutions to what can seem to be hopelessly complex problems.

Kenneth D. Herman, PhD, JD, is director of the division and both a psychologist and a lawyer. He noted that the program — located for eight years at the Judge Baker Guidance Center at Children's Hospital — was a natural to merge with the MGH Psychiatry and Law Service, founded in 1989 by Ronald Schouten, JD, MD (see *MGH News*, December 1990).

"Joining the two programs was really too good to pass up," he said. "We have a fine pediatric forensic [relating to the law] program, and Dr. Schouten has the definitive adult program. It only made sense to combine our efforts, and it is working out superbly."

Dr. Schouten added that, while his staff had been doing some work involving children previously, he was delighted to welcome Dr. Herman's team. "They are

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PHOTOGRAPHS: Pages 1,3,4,8 photographs, Susan McGreevey; Page 6 illustration, Arch MacInnes.

an outstanding group of people with a great reputation, good ideas, and a real devotion to the field. Their addition has greatly enhanced our ability to provide services."

In addition to Dr. Herman, the Children and the Law staff consists of Catherine M. Ayoub, MSN, EdD; child psychiatrist Donald Condie, MD; psychologist Robin M. Deutsch, PhD; and Robert T. Kinscherff, PhD, JD, also a psychologist/lawyer. It is one of the largest such programs in the country.

A frequent role for the Children and the Law staff is as court-appointed consultants in the sorts of cases described above. "Often these cases involve several people who want to raise the child," Dr. Herman explained. "Each of them may have strengths and weaknesses, and perhaps the child has special needs as well.

"Agencies such as the Department of Social Services or an adoption agency also may be involved, and the case may have become truly logjammed in the system. The court will ask us for help in understanding the many factors involved and coming up with a recommendation."

Other frequent consultations may involve juvenile crimes — helping the court take into account the psychological factors behind delinquency — and lawsuits involving incidents of psychological damage to a child. The program also has a supervised visitation service to provide safe access and continuing contact between parents and children.

In addition to being called on by the courts, staff members have been brought in at the request of an attorney in a case. However, they rarely become involved unless all parties agree on their participation.

"The common thread in all our work is that we have knowledge about how children develop and how that development can go wrong. It is our job to help the legal world — both the courts and the legislature — understand those factors and incorporate them into decisions that affect children," Dr. Herman explained.

The group actively consults to the Massachusetts state legislature on bills affecting children. In addition several of them conduct research in related areas. Dr. Kinscherff has published widely on post-traumatic stress in children and Dr. Ayoub has investigated the psychological development of maltreated children.

Educational activities are targeted to both mental health and legal professionals and range from in-house rounds and lectures at the MGH to workshops for statewide lawyers' associations.

Dr. Herman explained that the Western legal system has a very difficult time dealing with the reality of psychological development. The law frames issues from a very straightforward, yes-or-no perspective. But within a family, issues become very complex, and simple answers may be inadequate.

"You can certainly ask whether or not a mother abused her child. That is an absolutely appropriate question from a legal point of view, and the answer can be she did or she didn't. But when the question becomes, 'And what are we going to do about that,' legal reasoning fails dismally," he said.

The simple answer — to punish the mother by putting her in jail — brings up a whole host of new issues. Who will now take care of the child? Would the child feel responsible for the mother's incarceration?

Any circumstances that may have led the mother to abuse her child are only marginally considered. "What if the mother lost control with her child because she herself was being beaten?" Dr. Herman asked. "As it stands now, the law does not consider such factors, it simply asks 'Did you or didn't you do it?' "

What a psychological perspective can bring to these legal cases is an understanding of their complexity — the fact that any change within a family affects every aspect of that family and everyone in it.

"In cases of child sexual abuse, it is understood that the child's personal and sexual integrity are absolutely paramount," Dr. Herman said. "But what are the consequences of destroying that child's relationship to a parent?

"We try to figure out how to balance all those factors, how to reconcile the many — often conflicting — interests of the child. Sometimes we are successful, and sometimes we aren't."

A fundamental flaw in our legal system, Dr. Herman believes, is that children have no constitutionally guaranteed rights. That problem is now being recognized through the efforts of several national child advocacy agencies and should get even more attention because of the interest of new First Lady Hillary Clinton.

"As the legal system comes to grapple with the place of children in our society, I believe that programs like ours — with individuals who are informed about the development and psychopathology [mental illnesses] of children, as well as about the legislative and court systems — will have a huge contribution to make."

*Staff members of the MGH Children and the Law Program (from left) Donald Condie, MD; Robin Deutsch, PhD; Kenneth Herman, PhD, JD; and (far right) postdoctoral fellow Lynda Field, PhD, confer with Director of Law and Psychiatry Ronald Schouten, JD, MD (second from right). Not pictured are Catherine Ayoub, MSN, EdD, and Robert Kinscherff, PhD, JD.*

If these issues are not addressed, Dr. Herman added, the consequences could be dire. The signs are already seen today: children who pass from an overworked foster care system to the juvenile justice system to adult prisons; teenage gang members who terrorize whole neighborhoods; young boys who beat or murder their girlfriends.

"I think that as a society we've finally become so terrified of what we've created that we might actually be willing to pay attention to what's been done to children," Dr. Herman said.

"There are many people and groups that have been trying to address this issue for years. With the new visibility that Mrs. Clinton will bring, I have a lot of hope that we can begin to turn the situation around." ■

(Continued from Page 1)

test their resourcefulness in a crisis.

(The term anesthetist refers to a health care professional — a physician or a nurse — responsible for administering and monitoring anesthesia during an operation. An anesthesiologist is a physician who has completed specialty training in anesthesia.)

"Patient safety has always been a major concern of anesthesiologists, mostly because when things don't go well with anesthesia, patients can be hurt very seriously," said Richard J. Kitz, MD, Chief of the MGH Anesthesia Department.

General anesthesia — the complete lack of consciousness induced in patients undergoing major surgery — is the major focus of concern for patient safety. Modern anesthesia techniques can render a patient completely paralyzed, as well as insensible to pain. Anesthetists are responsible for maintaining patients' heart rate, respiration, blood pressure, the level of oxygen in the blood — literally keeping them alive during the surgery.

***Over the past two decades, several members of the MGH department have significantly contributed to national efforts to improve patient safety during anesthesia.***

During the 1970s a group led by Jeffrey B. Cooper, PhD, and Ronald S. Newbower, PhD (now MGH Vice President for Research Administration and Technology) conducted several studies analyzing the kinds of mistakes that occurred during anesthesia in several Boston teaching hospitals.

"Most of the time these mistakes didn't hurt anybody," said Dr. Cooper, who is Director of Anesthesia Technology and Biomedical Engineering. "But this was a way to study human error and identify how people made mistakes and how mistakes might be prevented."

The studies also helped to raise general awareness about what are called anesthesia mishaps. Concern reached a peak in the early 1980s when malpractice rates soared for anesthesiologists and several other categories of medical specialists.

In direct response to the issue, Drs. Cooper and Kitz — along with Ellison C. Pierce, Jr., MD, chief of anesthesia at New England Deaconess Hospital — organized a 1984 international symposium addressing the prevention of anesthesia mishaps. One result of that meeting was the creation of the national Anesthesia Patient Safety Foundation, with Drs. Pierce and Cooper in leadership roles.

At about the same time, the Harvard anesthesia chiefs created a committee with representatives from five major teaching hospitals — Beth Israel, Brigham and Women's, Children's, Deaconess, and the MGH — and from Mt. Auburn Hospital. The committee's purpose was to examine anesthesia-related malpractice claims at the hospitals and judge how they might have been avoided.

"After our review, the group decided that the one thing that should significantly reduce serious patient injuries was the application of a set of consistent, basic standards for monitoring a patient's condition during surgery," Dr. Cooper said.

A set of standards to be followed by all Harvard anesthetists was created by a group of representatives from the five hospitals. An article describing the standards was published in the *Journal of the American Medical Association* and eventually became the basis for a national standard adopted by the American Society of Anesthesiologists.

"The promulgation of these standards — along with continued improvements in monitoring equipment — seems to have worked phenomenally well," said Dr. Kitz. "In some regions, malpractice rates in anesthesia have dropped in half."

The development of anesthesia simulators was another approach to patient safety. "Simulators aren't a new idea," said Dr. Kitz. "They were first tried 20 years ago. But their use didn't spread because they weren't as realistic as we needed and because primitive computer

*An anesthesiologist/trainee examines readings on an anesthesia machine and monitors, searching for clues to a simulated problem.*

technology kept costs too high.”

Dr. Cooper became acquainted with several simulator-development projects as a member of the executive committee of the Anesthesia Patient Safety Foundation, which evaluated research proposals. He was particularly impressed by the work of David Gaba, MD, and his colleagues at Stanford University and the Palo Alto VA Medical Center.

“What Dave Gaba has done is put the simulator in a real operating room, add people in roles of a surgeon and nurses to interact with the anesthetist, and create a course in anesthesia crisis resource management around it,” Dr. Cooper said.

Anesthesiologists from the MGH and other Harvard-affiliated hospitals visited Dr. Gaba’s center in 1991 to take his course. As a result, he was invited to bring his simulator to Boston last fall and to offer the course for a three-month period, the first time it would be applied on such a large scale.

Faculty from the five teaching hospitals — including Drs. Michael Bailin, William Eckhardt, Nathaniel Sims, and Stephen Small from the MGH — were trained as instructors.

Dr. Gaba originally began developing a simulator to study human performance and decision making by anesthesiologists. “But we realized that our work had training implications,” he said. “Based on the way simulators were used in other industries — most notably aviation — it was appropriate to employ them to examine how people think and respond in crisis situations.”

As Dr. Cooper noted, the Stanford simulator is set up in a regular operating room. A set of computers, attached to a standard anesthesia machine and patient monitors, controls many of the signals and readings displayed. A mannequin “patient” on the operating table is realistically ventilated by the equipment and can be treated in many respects like a real patient.

Adding to the reality of the situation are specially trained “actors” — usually staff physicians, resident physicians, or nurses — who play the roles of surgeons, operating room nurses, and anesthesia technicians (who maintain anesthesia equipment and may assist in an emergency).

An anesthetist going through the experience may have to deal with a simulated situation where a critical piece of equipment breaks down, where crucial information about a “patient” is unavailable, or where a “patient” has an unusual reaction to the anesthesia. In addition to analyzing and solving the problems, the anesthetist also must deal with the reactions and sometimes competing demands of the other members of the OR team.

“In the operating room you have many resources,” Dr. Gaba said. “You have your own expertise in anesthesia, the equipment, the other OR personnel, and external resources like the laboratories. The expert in crisis management can use all these resources to best advantage, not just concentrate on one of them.”

***“Even though this simulator is still rather primitive in many respects, most people say it feels like a real OR experience.”***

The simulator experience is only one part of the course. Participants hear a lecture on crisis management, view videotapes showing both a simulator reenactment of an airline crash and an anesthesia mishap in an operating room, and discuss the incidents they viewed in light of the principles they have learned.

The simulator sessions are also videotaped, and participants review their performance with the instructors in a two-hour debriefing session. Adam Sapirstein, MD, chief anesthesiology resident at MGH and a course participant, noted that viewing the videotape after the simulator session provided a unique perspective.

“You never see yourself giving anesthesia, so watching the videotape can be an insightful, even humbling experience,” he said. “In addition to major issues that come to light about your performance, little habits you might not be aware of can be a tipoff to others in the room that you are uncomfortable.”

Dr. Cooper, who observed many simulator sessions, said, “People really feel on the spot. Even though this simulator is still rather primitive in many respects, most people say it feels like a real OR experience.

“We invited Dr. Gaba here not just to put some of our people through the course but really to test whether we could train a group of instructors and pull together the necessary resources,” he continued. “We also wanted to expose more people to the concepts of crisis resource management.”

While no one claims that the simulator or the course do not need further refinement, the pilot program was enough of a success for the chiefs of the involved anesthesia departments to decide to jointly acquire a simulator. One should be in place at a participating hospital by mid- to late 1993.

“I think we’ve really answered the question of whether we can provide a realistic experience, similar to that of taking care of a sick patient in an operating room,” Dr. Kitz said.

However, Dr. Cooper notes, “We will eventually have to come up with ways to evaluate objectively what the use of simulators contributes to anesthesia education and safety.”

Dr. Kitz anticipates several eventual applications for fully developed simulator systems: training of residents and nurse anesthetists; giving experienced anesthesia professionals a chance to practice dealing with rare but dangerous events they might never see in normal practice; and testing new equipment to see that it is “user friendly” in a crisis.

“If we can convince people that the simulator is a tool that will enhance their performance and reduce the likelihood of making errors, I think it may become incorporated into the training process within this decade,” Dr. Kitz said.

“This has the potential of being the next big improvement in the quality of anesthesia care in this country.” ■

Social Phobia

# Fears That Can Constrict a Life

INTERVIEWING for a new job, walking into a new school, speaking before a group, meeting a blind date — all these situations can make someone nervous. It is only natural to feel those "butterflies in the stomach" when confronted with the possibility of being judged in terms of one's personality, attractiveness, and general competence.

But what if those feelings were so strong that they overwhelmed all other thoughts? What if they kept one from making friends, from succeeding at work, from enjoying personal interaction of any sort?

There was a time when people with such feelings would have just been considered overly shy. But more recently it has been recognized that they may have social phobia.

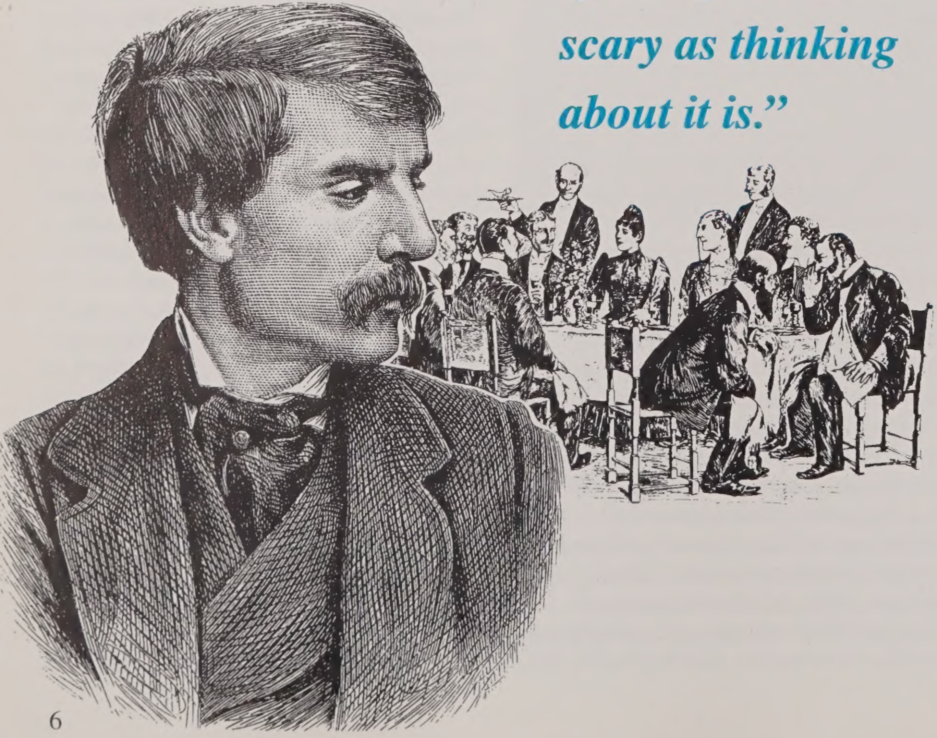
"People with social phobia have anxiety in social situations that causes them extreme amounts of distress and interferes with normal activities," said Mark Pollack, MD, Director of the Anxiety Disorders Program in the MGH Clinical Psychopharmacology Unit.

He noted that students with social phobia may fear speaking in class, even when confident of knowing the answer. Employees may turn down promotions to positions that would increase personal interactions.

"One thing that really differentiates normal social fears from social phobia is that people make major life changes to avoid the anxiety-provoking situations," he added. Alcohol and drug abuse frequently add to the difficulties of those with social phobia, who may use substances to mask their anxieties.

These are not people who simply choose an independent, solitary life, added MGH psychologist Michael Otto, PhD. "People with social phobia are kept from doing things they want to do. When they find themselves forced into social situations, they are miserable."

> ***"I'd tell anyone else with these fears that they're not alone, that it can be really helpful to work with others who have the same problems. Doing what you're afraid of doing is not as scary as thinking about it is."***



For some, social phobia arises only in specific situations — like public speaking or performing. But others are paralyzed by fear in the face of almost any potential personal interaction.

Social phobia most commonly begins in adolesence, but some seem to have been affected since they were children. Maryanne, a 28-year-old Boston-area woman, recalled that she had been fearful of any social situation since kindergarten.

"I always had a lot of negative thoughts about myself," she said. "It had a terrible effect on me in school. I didn't socialize; I always felt that I was different from everybody else."

Laura, a Maine woman in her early 30s, traces her fears to her junior high school years. "It really made for an isolating existence. I avoided situations that might not have been as bad as I thought they would be."

Causes of social phobia are not clear. Like most other anxiety disorders there may be a genetic basis, as the condition runs in families. But experience certainly plays a part.

"It's normal to be excited and nervous in social situations," Dr. Otto explained. "For most people that arousal directs attention to the social cues given by others, to what they are discussing; and they function just fine.

"In people with social phobia, such arousal brings out thoughts like, 'What are people thinking of me? Am I going to do something stupid?' They can't help but be anxious."

He added that some with social phobia do lack important interpersonal skills, probably because fears prevented skill development. Others actually function rather well, but are excessively critical of their own performance.

While social phobia's effects can be devastating, there is a positive outlook. Several treatment strategies — specifically medication and behavioral therapy — have helped patients overcome their fears. Antidepressant or antianxiety drugs can lessen the anxiety reaction and may help to break the cycle of negative thinking that traps those with social phobia.

"Some of the older antidepressants, particularly monamine oxidase inhibitors, are very effective. But they have some side effects and may interact with certain foods," Dr. Pollack said. "We are investigating new versions of these drugs that place fewer restrictions on patients."

Maryanne participated in a four-month trial of one new drug and reported significant improvement. "I'm feeling pretty good now. Talking to people used to give me a lot of anxiety, and now I can deal with it better."

Behavioral therapy directly addresses the thoughts that plague patients and helps them understand how their anxieties are linked to negative self-evaluation. Patients learn new ways of interacting and can try them out in a supportive environment.

Some behavioral therapy takes place in group settings. One such group meets at the MGH weekly for 12 weeks. The group gives participants a built-in audience before which they can practice social skills.

Dr. Otto explained, "Patients get a chance to anticipate their negative thoughts and to act in spite of them. They find that even though they were anxious, they performed well. That means that the next time they face a similar situation, they will have a positive memory to fall back on."

Laura, who participated in a recent group, described how members help each participant develop a "rational response" — a competing thought to replace the automatic negative thoughts — before acting out a stressful situation.

"During role-playing, every 60 seconds the action stops, and we repeat our rational response out loud. I found that very helpful, and it's helped me prepare for real situations before they come up," she said

***One question yet to be answered is whether medication, behavioral therapy, or a combination of the two works best — or if different treatment plans are better for different patients. A new MGH study directly addresses that issue by comparing patients' progress on the two types of therapy.***

"What's happening with treatment of social phobia is similar to what happened with panic disorders in the 1980s," Dr. Otto said.

"The different approaches of the two disciplines — medication from psychiatry and behavioral therapy from psychology — are being brought together in a healthy competition to see what really works best for the patient." (For more information about the research studies or social phobia treatment, call the MGH Anxiety Disorders Program at 617 726-6944.)

The fact that most people sometimes feel anxious in social situations has often led to a lack of understanding for those with true social phobia, Dr. Pollack added.

"This really is a different entity from normal anxiety. Many people with social phobia have been made to feel that their problems were their fault. That it was something they could handle if they were tougher. But this is a real disorder of function. and effective treatment is available."

Laura expressed a feeling shared by many recovering from social phobia when she said, "I feel like I'm just starting to come out of hiding.

"I'd tell anyone else with these fears that they're not alone, that it can be really helpful to work with others who have the same problems. Doing what you're afraid of doing is not as scary as thinking about it is." ■

# Family Doctors for the Next Century

THE FAMILY DOCTOR — who treats everyone from the newborn baby to the great-grandmother — may seem to belong more in a Norman Rockwell painting than in today's high-tech medical world.

But a group of resident physicians at the MGH is learning to be the family doctors of the twenty-first century. They are members of the Combined Program in Medicine/Pediatrics.

Established three years ago, the combined program is an offshoot of the primary care residency offered through the MGH General Medical Services. It is one of several joint medicine/pediatrics residency programs in the country, and the only one currently offered in the Boston area.

The four-year program prepares residents to board certify in both internal medicine and pediatrics. It differs from a family practice program in that it does not include training in obstetrics.

Program Director Laurence J. Ronan, MD, explained that such a residency appeals to two types of physicians.

"There are doctors who want to take care of entire families, providing all primary care health services," he said. "Others want to subspecialize in a field that cares for people of all ages — such as congenital heart disease, rheumatology, or infectious disease."

Dr. Ronan actually blazed a trail for medicine/pediatrics training at MGH soon after he became a primary care resident in 1987. He realized that he wanted to pursue his interest in pediatrics in a more formal way without abandoning studies of adult primary care (the focus of internal medicine).

With the cooperation of the Medical Service's primary care program and the Children's Service, he worked out a specialized schedule involving training in both services. Despite the bureaucratic tangles that resulted from combining elements of separate programs, he had "a wonderful experience in both services."

Based on both Dr. Ronan's example and a growing national interest in combined medicine/pediatrics programs, the two services decided to offer a formal, combined program beginning in 1990.

The residents train for four years — instead of three as in the regular medicine and pediatric residencies — spending equal amounts of time in both areas.

"We try to eliminate as much overlapping material as possible to give them a complete core experience in each discipline," Dr. Ronan explained.

Following the model of the primary care residency, participants in the combined program spend about 25 percent of their time working in ambulatory care settings — specifically at the MGH-affiliated health centers in Revere and Chelsea.

Roger Pasinski, MD, is Assistant Program Director and on the staff at MGH-Revere Health Associates. He trained in a joint medicine/pediatrics program at the University of Rochester and arranged to bring two of the first MGH combined program residents to Revere for their ambulatory training.

"Medicine and pediatrics have a long, strong history of working together at Revere, as the center is small and we're located on the same floor," he said. "I've had a strong interest in combined training programs and always felt that MGH would be an excellent place to develop one."

Four medicine/pediatrics residents now

*(Concluded on Page 8)*

## — Family Doctors

*(Concluded from Page 7)*

spend one half-day a week at the Revere clinic, and two work at the MGH-Chelsea Health Center. Another works in Dr. Ronan's clinic at Internal Medicine Associates in the Wang Ambulatory Care Center.

"The residents essentially apprentice themselves to the health center physicians," said Dr. Ronan, who also works at Chelsea. "They receive a lot of support from the senior physicians but are responsible for taking care of their own patients. It works out beautifully; someone will see a two-week-old baby and then see that child's grandmother a month later."

Both of the health centers serve culturally and socially diverse populations, presenting residents with an array of challenges. First-year resident Anashua Sinha, MD, works at Chelsea. She noted that the city, long a gateway for immigrants, today includes many new arrivals from Central America.

"The most simple health needs of many of these people have not been met in the past. Even adults need basic immunizations and screenings. In addition, they may be without the social supports that most of us take for granted. It's challenging and satisfying to help them," she said.

Dr. Sinha, who plans to go into public health, added that the combined residency was an ideal option for her. "Anyone who wants to study public and community health needs to understand the full range of problems affecting both adults and children."

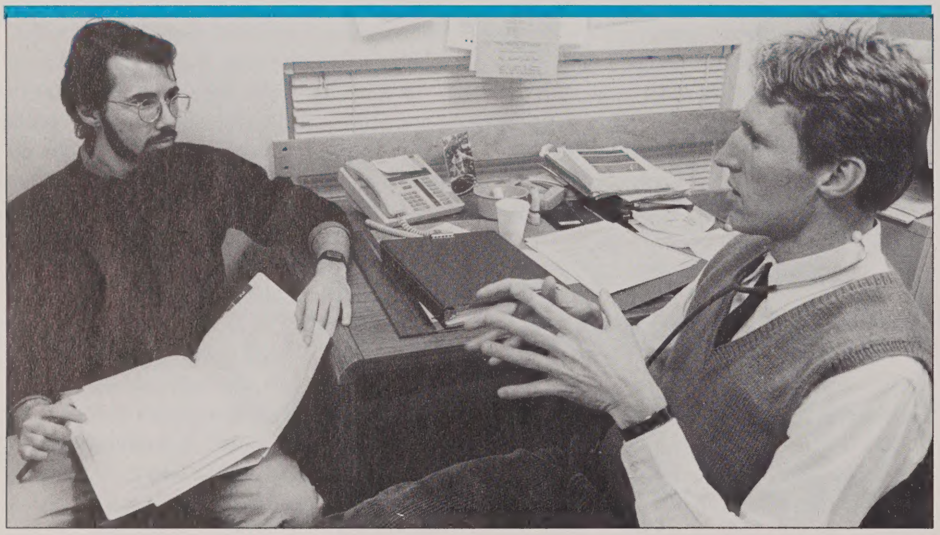
Andy deFreitas, MD, one of the first medicine/pediatrics residents, is now in his third year. Located at Revere, he noted, "When you come to a center like this, you become identified as part of the community, which is nice.

"I'm now trying to decide on the next step in my career, which is difficult because I'm interested in both primary care and specialty work. But whatever I end up doing, it will be with both adults and children."

Dr. Ronan hopes that the combined program can make a contribution to meeting some of today's most critical health needs — more primary care physicians and more attention to community health needs. He also believes the opportunities available to graduates of such a program can be uniquely satisfying.

"I see it in my own practice," he said "Children I cared for as infants are now starting school; teenage girls are now young mothers. It's all about the enjoyment of taking care of patients at every stage of the life cycle. Helping members of a family through major life events — from welcoming a new baby to losing a parent — creates a powerful, positive psychological bond."

And the MGH program has special strengths not found elsewhere, he adds. "We combine the excellence of our established residency programs; the top-notch, academic tertiary care experience; and the opportunity to serve a very diverse population in the health centers. Our niche is small, compared to the larger mission of the hospital, but it has its own very special value." ■



*At MGH–Revere Health Associates, medicine/pediatrics resident Andy deFreitas, MD, discusses a patient's situation with Roger Pasinski, MD.*

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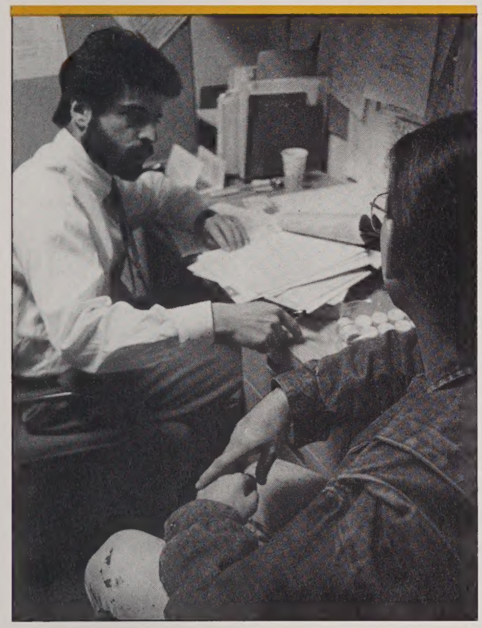
# Reaching Out to Care for the Homeless



*Dr. Michael Bierer reviews medication instructions with a homeless patient in the Medical Walk-In Unit.*

***Get this prescription filled; rest in bed for three days; and come back in a month.***

SUCH instructions would be easy to follow for most of us. But what if you had no money for medications? What if you were turned out of your dwelling every morning, no matter the weather? What if you had no idea where you would be in a week, much less a month? What if you were homeless?

Homeless people always have been cared for at the MGH as inpatients and outpatients. But the profound disruptions in their lives made it difficult for them to take full advantage of services available to them. With every day a struggle to find adequate food and shelter, few homeless people can address long-term health issues.

The MGH Medical Program for the Homeless was established in 1988 to coordinate services for the growing number of homeless patients and to develop expertise in dealing with their unique problems. It is part of the Boston Health Care for the Homeless Program (BHCHP), a city-wide effort operating a network of medical clinics in shelters, soup kitchens, and welfare hotels.

MGH was the first, and for several years the only, private hospital to work regularly with BHCHP. (Physicians at the Brigham & Women's Hospital have recently shown an interest in developing similar programs.) As would be expected, the public Boston City Hospital is also an integral part of the program.

The MGH effort involves an interweaving of several activities: coordinating services for homeless patients admitted as inpatients, providing outpatient care through the Medical Walk-In Unit, and reaching out to people in shelters and on the streets. This last element can be crucial in bringing people into the system.

"Without the clinics at the shelters and the nurses who run them, many homeless people wouldn't feel comfortable enough to discuss their problems and seek any

*(Continued on Page 2)*

# *MGH Scientists Pursue Clues to the Mystery of Alzheimer's*

The tragedy of Alzheimer's Disease — with its relentless loss of memory and reasoning — is matched by its mystery. The disease's distinctive features are well known, but scientists vigorously debate their significance and relation to the disease's progression.

The brains of people with Alzheimer's show an overall loss of brain tissue. A substance called beta amyloid accumulates in plaques throughout the brain. Tangled filaments of protein appear inside brain cells.

In addition, levels of neurotransmitters — chemicals that carry messages between brain cells — are reduced. Major deficiencies occur in acetylcholine (a substance known to be important in memory) and in proteins involved in production of acetylcholine.

MGH neurologist John H. Growdon, MD, directs the Massachusetts Alzheimer's Disease Research Center, headquartered at the MGH. The center is a consortium of the Harvard-affiliated hospitals, the Harvard Division on Aging, the Mass. Institute of Technology, and the University of Mass. Medical Center.

Several MGH researchers affiliated with the center are searching for clues to the causes and development of Alzheimer's in the interplay of genes, molecules, and cells that underlies the workings of the brain.

Up to 25 percent of those with Alzheimer's belong to families with a history of the disease, which suggests an inherited cause for those cases. To find a gene responsible for an inherited disease, scientists examine the chromosomes — tightly wound bundles of genes — of affected and

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EDITORIAL

## Failure or Seed that Flowers?

YUNG-KANG CHOW is an MD-PhD candidate at Harvard Medical School. He works long hours in the laboratories of the MGH's Martin S. Hirsch, MD. Nothing unusual about that. As head of the MGH Virology Laboratory, Dr. Hirsch regularly has one or more young students and fellows there to learn science.

One day Dr. Hirsch assigned Mr. Chow to review a grant concerning why two commonly used AIDS drugs retained their ability to work against strains of the AIDS virus that had developed resistance to one of them. As Mr. Chow was reading Dr. Hirsch's research papers at the dinner table, an idea demanded total attention. Until then physicians used a combination of drugs to attack the AIDS virus at different points of its process of reproducing itself. Maybe that, Mr. Chow thought, gave the virus the opportunity to mutate or change itself into a variant which could resist each drug. Suppose that instead several AIDS drugs were used simultaneously to assault the virus at **one key point**. Many laboratory leaders would have dismissed the idea as too removed from conventional thinking. "Let's see if it works," Dr. Hirsch said.

In the coming months, Mr. Chow planned the attack with the intensity of a military commander about to wage war. Evolution has made very simple the mechanism by which the AIDS virus changes itself into a drug-resistant form. Perhaps so simple that an all-out assault on that one point could overwhelm it. The vulnerable point is one where the virus changes one type of genetic material into another, a transformation that is essential to reproduction of the virus.

Mr. Chow planned to use three AIDS drugs at that key point at which the process called reverse transcription takes place. But carrying out the scheme involved more attention to detail than most nonscientists could imagine. Some senior members of the team shadowed each move Mr. Chow made. With every new finding they challenged Mr. Chow to produce the supporting evidence. Lesser men would have crumbled under the constant pressure. But Mr. Chow proved he had resiliency as well as creativity. He'd bounce back with the data in hand and then return to his next experiment. Richard T. D'Aquila, MD, a molecular virologist and AIDS clinician, was particularly relentless in assuring that no tempting shortcuts were even considered. Joan C. Kaplan, PhD, was also at Mr. Chow's side to challenge and assist. Joseph J. Eron, MD, and Lawrence J. Bechtel, a research technician, sometimes assisted in particular experiments. And Debra P. Merrill, a senior research technologist of consummate skills, was always there to guide Mr. Chow. Making certain that the entire laboratory was constantly performing with the elan of a symphony orchestra was the conductor, Dr. Hirsch.

The study at last over, every detail of data scrutinized, it appears to show what Mr. Chow had predicted. By bombarding that vulnerable location with three potent drugs at once, the scientists reduced the simple mechanism to a scrap heap no longer able to reproduce itself.

The resulting article in the British scientific journal *Nature* is history. So are the front-page newspaper articles and the network television and radio accolades. Now Drs. D'Aquila and Hirsch are about to lead a national trial to determine if the pupil's test-tube success will stand up against the reality of the ultimate test, the complex human bodies of victims of the AIDS virus. If those trials verify the work done in the test tube, they will be expanded to include still more patients. Only then will the world know if Mr. Chow's inspiration was a brilliant idea which failed when faced with the complexities of the real world. Or a seed that flowered into a wonderful new treatment. Or something in between. ■

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## — Homeless

*(Continued from Page 1)*

sort of health care," said Michael Bierer, MD, MPH, director of the Medical Program for the Homeless.

Dr. Bierer, his colleague Roseanna Means, MD, and other BHCHP doctors each spend several days a week at Boston-area shelters, getting to know the clients and seeing to immediate medical needs. "There's a certain kind of interaction we can have with patients on their own turf that would be difficult in the hospital environment," he explained.

Dr. Means added that taking the time to make personal contact with homeless people is a prerequisite for dealing with their health problems.

"Often all I do when I first meet people at a shelter is just talk — find out about their background, how they became homeless, what issues have affected their lives. It takes time for them to become comfortable with me as a person and not someone who's going to challenge or judge them," she said.

The Medical Walk-In Unit is a primary setting for providing continuing care for the homeless. Any patient — homeless or not — can be seen without appointment. Drs. Bierer and Means each spend one day a week in the unit, specifically to see homeless patients referred from shelters or following up previous visits.

"The nurses in the unit have become well geared toward caring for our patients," Dr. Bierer said. "At the same time, our clinic is basically invisible within the unit. The patients aren't separated from the other walk-in patients or stigmatized in any way. And they have

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PHOTOGRAPHS: Pages 1,3,4,5,7 photographs, Susan McGreevey; page 6 photograph, Marjorie Siegel.

full access to other services offered by the hospital."

Homeless people admitted to the MGH — either through the walk-in unit or the emergency room — are cared for on whatever inpatient floor their needs dictate. Kathleen Cumming, RN, MS, gerontological clinical nurse specialist, works with the homeless program team and with unit nurses to help optimize patient care.

"A lot of what I do is fostering an understanding of the homeless through communication with nurses. My goal is to be a role model to other nurses, helping them to see the real person behind issues of homelessness or substance abuse and deal with the frustrations of trying to help people who can have so many problems," she said.

Ms. Cumming works closely with members of the Social Service Department on the challenging issue of discharge planning. One of their major concerns is the most basic — where will a homeless person go after discharge from the hospital? Coordination with shelters can ensure that a patient has a bed for the night. When necessary, special arrangements can allow a recovering patient to stay in the shelter the following day. (Shelter clients usually must leave each morning.)

Social worker Linda Kane helps Medical Walk-In Unit patients gain access to available services in the community. "My role is to make sure they keep connected, to get them through the red tape involved in Medicaid, Medicare, Social Security, and medication programs. I can also make referrals to detoxification and substance abuse programs."

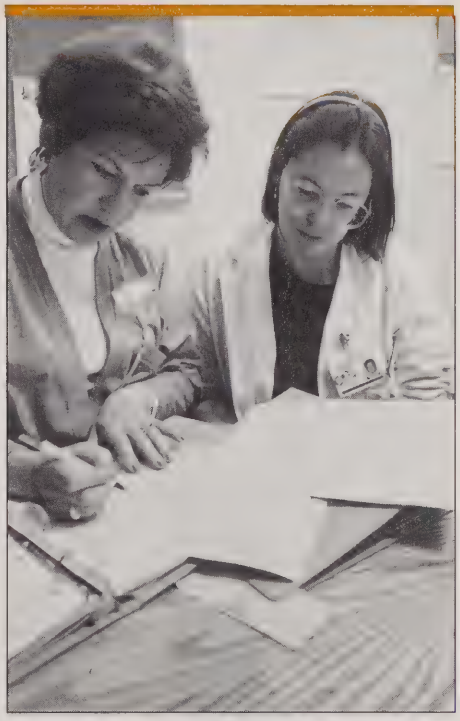
Substance abuse is certainly a significant issue for many — although not all — patients seen through the homeless program. "When people are out of control with their substance abuse, it's very hard to help them with other health problems," Dr. Bierer admitted.

"But you really have to let *them* call the shots, they have to be ready to work toward getting sober. Letting the patient set the agenda is important for anyone; but it's particularly crucial for the homeless. You have to address what's on their mind today, which could be getting a warm pair of socks or something to eat."

Patients actually can get some of those basic needs filled at the MGH. A shoe bank in the Emergency Room distributes new sneakers contributed by several manufacturers. Sweatsuits donated through Social Service also are available to homeless patients.

Working on the more difficult issues can be frustrating. "If someone in the Emergency Room wants a referral to a detox facility after 12 noon, I can pretty much guarantee that there's no bed available for them that day," Ms. Kane said.

Dr. Means added, "Medicine can be very difficult no matter what population you deal with. When I was in private practice, I had patients who drank too much, smoked too much, whatever. Frustration is not unique to taking care of homeless people."



*Kathleen Cumming, RN, (right) discusses discharge plans for a homeless patient with Bigelow 10 staff nurse Ellen Daley, RN.*

"You really have to keep in mind what is reasonable," Dr. Bierer stressed. "I ask patients where I can call them with test results, what shelters they may be staying at, is there a relative or a shelter worker who can be a contact? Shelter clinics are invaluable in helping monitor whether they're taking medication and reminding them of followup appointments."

That issue — what is reasonable? — colors many aspects of care for the homeless. It describes the kind of perspective that must be maintained in judging whether efforts on behalf of a patient — beyond simple treatment of an acute injury or illness — can be termed successful.

As a result, success is looked for in small steps that can represent the result of considerable effort, coordination, and patience. These can include convincing a patient who is suspicious of doctors or hospitals to have a life-threatening problem cared for, supporting a substance-abuser through repeated efforts to maintain sobriety, or connecting someone with the community agency that finds just the right living situation.

For example, MGH social workers were able to obtain a housing subsidy for a man who had been living in a railroad box car for several years; he is now living in an apartment. A woman with paranoia refused to have a cast removed from her leg for more than a year. MGH doctors and shelter outreach workers together convinced her to have the cast taken off and return to the hospital for followup visits.

"I think part of what we do is not 'medical' in the traditional sense," Dr. Bierer said. "It's helping people make some sense out of their existence and value their lives. Creating a space where people can restore a sense of their own dignity and self-worth is an essential first step toward helping them pay attention to their health."

Dr. Bierer credits many people at the MGH for the success of the homeless program. They include John Potts, MD, chief of Medical Services, who supported the program's establishment; Britain Nicholson, MD, former director of the Medical Walk-In Unit; Richard Pingree, MD, associate director; Barbara Woo, MD, the current director; Nancy Bryant, RN, nurse manager; and the unit's nursing staff.

Another important player is James O'Connell, MD, an MGH physician who now directs the overall BHCHP. "We really see the MGH as the most accessible, easiest private hospital for homeless patients to use," he said. "The MGH sets a great example for other private hospitals by showing how participating in a coordinated program like this can improve delivery of care to people who were using their services to begin with."

Dr. Means agrees: "I can't imagine an inner-city hospital in the 1990s ignoring the homeless population in any concerted way. But to have an institution the size and power of the MGH recognize this need and give us the kind of support we've received is just fantastic," she said.

"One of the things I've learned here is that there is no typical homeless person," she added. "There are the alcoholics and drug addicts, but there are a lot of people who've just been very unlucky and find themselves living in a shelter. Everyone who walks into the hospital — whether they are homeless or live on Beacon Hill — is our responsibility. We're here to take care of them; it's our mission as doctors." ■

# — Alzheimer's Disease

*(Continued from Page 1)*

unaffected family members.

They search for markers associated with a possible Alzheimer's gene. Markers are sequences of DNA — sequences that can vary slightly from person to person — known to appear at a specific location on one of the 23 sets of human chromosomes.

If a particular marker variation is seen in family members with a genetic disease but not in unaffected people, and the variation appears to be passed on with the disorder, it is highly probable that the disease gene and the marker are located near each other on the same chromosome.

In 1987, MGH researchers Peter St. George-Hyslop, MD; James F. Gusella, PhD; and Rudolph E. Tanzi, PhD, led an international team that linked inherited Alzheimer's with an abnormality on chromosome 21. They later showed that genetic defects involving other chromosomes are associated with some cases of familial Alzheimer's.

Researchers at Duke University found that some late-onset cases are associated with chromosome 19. Most recently Dr. Hyslop (now at the University of Toronto) and Dr. Tanzi were among the first to find a probable early-onset gene defect on chromosome 14.

Pinpointing the exact genes that cause inherited Alzheimer's and finding out how they change the chemical activity of brain cells is a focus of Dr. Tanzi's current work.

Researchers elsewhere showed that the defect on chromosome 21 is in the gene that codes for a molecule of great interest: the amyloid precursor protein (APP). Dr. Tanzi's team was among the first to clone the APP gene and now is investigating how the gene's abnormality affects the protein's function and processing.

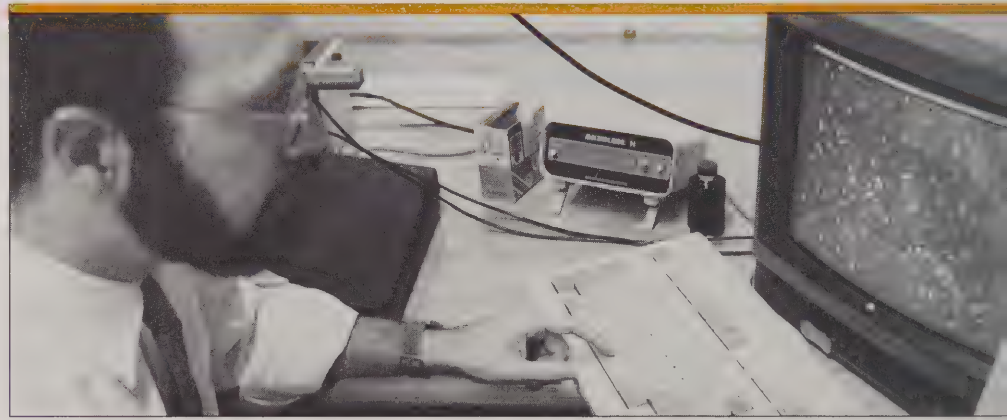
Processing refers to the way proteins are changed during their life in the cell. They are folded into special shapes, segments from the original chain can be removed, and the entire protein may be split into several smaller pieces.

APP contains a segment that, when removed from the complete protein, forms the beta amyloid found in Alzheimer's plaques. It is believed that APP can be processed in several ways — some that release the amyloid fragment and some that do not.

The familial Alzheimer's gene on chromosome 19 has not yet been identified, but one possible culprit has been discovered by Wilma M. Wasco, PhD, in Dr. Tanzi's lab. "This gene is very much like the APP gene in its structure, particularly in regions that may be involved in the still-unknown function of APP," she said.

The product of this new gene, called amyloid-precursor-*like* protein, does not contain the beta amyloid region. However, Dr. Wasco suspects that the new protein may share similar functions with APP and be processed by some of the same chemicals.

It is possible that mutation-induced changes in the function or processing of amyloid-precursor-like protein could have an impact on the function or processing of APP, leading to release of excess beta amyloid. Drs. Wasco and Tanzi are currently searching for mutations in this new protein that may lead to familial Alzheimer's.



*Dr. Bradley Hyman examines an image of the protein tangles found in brain cells of people with Alzheimer's Disease.*

The exact role of beta amyloid in Alzheimer's is one of the hottest topics in the field. Does it cause the death of brain cells? Is it is a byproduct of other destructive processes?

Dr. Growdon believes that evidence to date is inconclusive and that further understanding of how amyloid plaques form will reveal as-yet unexpected complexities.

"Several groups have recently shown that a soluble form of beta amyloid [one that does not form plaques] is normally produced in the body. We're going to have to rethink a lot of our assumptions," he said.

Roger M. Nitsch, MD, a research fellow of Dr. Growdon's, studies amyloid in the M.I.T. lab of Richard J. Wurtman, MD, who is also on the MGH staff. Dr. Nitsch recently published the first report showing a relationship between beta amyloid formation and activity of the neurotransmitter acetylcholine.

The usual processing of APP cuts right through the portion that forms beta amyloid. This splits the amyloid fragment in two, preventing the formation of plaques. Apparently, an alternative processing occurs more frequently in Alzheimer's, freeing beta amyloid to solidify into plaques.

Dr. Nitsch and his colleagues decided to look for a relationship between APP processing and acetylcholine activity. They found that stimulation of two types of acetylcholine receptors (structures that receive chemical signals) increased the processing of APP that does not release amyloid.

It may be that the lower levels of acetylcholine and other neurotransmitters seen in Alzheimer's increase the amyloid-releasing type of processing. But Dr. Nitsch cautions that neurotransmitter-to-cell communication is very complicated.

The defect leading to amyloid deposits could also involve the receptor itself or the series of chemical reactions that leads from receptor activation to protein processing.

***"This discovery suggests possible preventive or treatment strategies using drugs that stimulate the receptors," he said. "But we need to learn a lot more about how neurotransmitter receptors influence protein processing."***

Amyloid plaques and protein tangles are found throughout brains affected by Alzheimer's. But the abnormalities and attendant loss of brain tissue are most extensive in certain areas. These structures are involved in memory and learning.

MGH neurologist Bradley T. Hyman, MD, PhD, has been studying what happens within these structures and has found that only certain neurons (nerve or brain cells) seem to be affected. These

neurons project from memory-related structures into other parts of the brain, carrying messages back and forth.

It is as though the cables running from a central computer to outlying terminals were progressively damaged. New information added at the terminals might become garbled or not get to the central computer at all; data stored in the central computer could not always be retrieved. Eventually the connection between the terminals and the central computer completely breaks down and communication ceases.

***“Previously it was believed that Alzheimer’s affected the whole brain equally and that there was a decline in all cognitive [thinking] functions,” Dr. Hyman explained. “We’ve shown that it’s really a case of selective vulnerability.***

***“Just as only certain neurons are affected, the dementia seems to involve specific abilities as well. But these impairments — in memory and language — make it difficult to test the abilities that remain.”***

Dr. Hyman also investigates the protein tangles that appear inside affected nerve cells. “It seems clear that having this tangle of protein inside isn’t doing the cell any good,” he explained. “But there is no real evidence of what happens inside these neurons.”

He and his team have been measuring biochemical changes in brain tissue from people who have died with Alzheimer’s, changes that indicate whether neurons were receiving normal signals from adjacent cells. While it does appear that cells with tangles do not receive signals correctly, there is much to learn about exactly how that abnormality arises.

Another possible angle for cell damage in Alzheimer’s is being investigated by neurologist M. Flint Beal, MD. His early research helped to define some of the changes in neurotransmitter activity in the disease. Now he and his colleagues are examining possible involvement of the cell’s energy mechanism.

Specifically they are focusing on mitochondria, the cell’s internal power plant. Mitochondria are unique among structures found within cells in that they have their own DNA, separate from the DNA found in chromosomes.

*Drs. Rudolph Tanzi and Wilma Wasco investigate the relation between certain genetic abnormalities and inherited Alzheimer’s.*

It has been shown by researchers — including Dr. Beal and collaborators at Emory University — that mitochondrial DNA becomes damaged during normal aging, which may make the aged more susceptible to the Alzheimer’s processes. Most recently his group discovered small mutations in mitochondrial DNA in some Alzheimer’s patients.

Dr. Beal explained that changes in mitochondrial activity could damage neurons by reducing production of ATP, the substance that provides energy for many essential cellular reactions. One role for ATP is to maintain the normal electrical charge of the membrane that surrounds each cell.

This charge controls how easily neurotransmitter receptors can be activated. A change in receptor sensitivity could cause a type of overstimulation that leads to cell damage and death.

Although no effective treatments for Alzheimer’s are known, several patient studies are carried out through the Alzheimer’s Disease Research Center. At MGH, these include imaging studies of brain biochemistry in living patients, analysis of memory and sensory defects, and distinguishing inherited from noninherited forms of the disease.

In addition, several MGH researchers not directly part of the ADRC have Alzheimer’s studies — including Marilyn S. Albert, PhD, who investigates memory loss in both Alzheimer’s and normal aging.

Joseph T. Coyle, MD, chairman of the combined Harvard Medical School Psychiatry Department (which includes the MGH service), is working on an animal model for Alzheimer’s. His team has been pursuing the observation that people with Down Syndrome always develop Alzheimer’s in midlife.

This is particularly significant because Down’s is caused by a tripling of chromosome 21. (It is normal to inherit two copies of each chromosome). As noted above, this chromosome includes the APP gene and was the first to be linked with an Alzheimer’s gene.

Dr. Coyle’s group has developed a mouse model with a triplication of chromosome 16, which carries many of the genes found on human chromosome 21. These mice develop extensive nervous system abnormalities that prevent their survival. But studying how these defects interact to destroy brain cells may help to clarify the role of amyloid and other abnormalities in destroying brain cells in Alzheimer’s.

Basic laboratory research may seem far removed from the emotionally wrenching demands of caring for people with Alzheimer’s. But Dr. Growdon notes that many of these scientists also see the disease’s devastation first-hand.

“We have a tightly knit, highly focused group of people who are both clinicians and investigators,” he said. “They see patients on a weekly basis and can carry their knowledge from the clinic into the laboratory and back again.

“Eventually we apply what we’ve learned in both locations to the third leg of research — therapy. Through trials of drugs that affect the processes studied in the lab, we may find ways to slow down or stop what is now an irreversible process of mental decline.” ■

# Professorships Embody Link Between MGH and Harvard

*Drs. Marshall Bartlett and Claude Welch at the Harvard reception celebrating the new professorships in their honor.*

THE establishment last fall of Harvard Medical School professorships named for surgeons Marshall K. Bartlett, MD, and Claude E. Welch, MD, forged the two most recent links in a chain that connects the distinguished histories of both the MGH and the medical school.

Named professorships or "chairs" are among the highest honors that can be bestowed on academic faculty in any discipline. The first donation toward the establishment of Harvard Medical School — a 1770 bequest from physician Ezekiel Hersey — was used to establish professorships in medicine and surgery. The two physicians who co-founded the MGH — John Collins Warren and James Jackson — were among the first Hersey professors.

The hospital and medical school grew in tandem during their early years. For much of the 19th century the school was located across the lawn from the hospital's Bulfinch Building. Leading MGH physicians held the most prestigious chairs and played major roles in running the school.

MGH set the pattern for Harvard-affiliated hospitals by remaining an independent institution, with its own board of trustees, administration and employees. Some of the earliest professorships shifted to faculty at "newer" teaching hospitals, established around the turn of the 19th century. Additional chairs were established to honor such MGH luminaries as Dr. Jackson, James J. Putnam, and George C. Shattuck.

A named professorship represents an endowment, a sum of money held by the university, the interest from which supports research and teaching activities of the faculty member appointed to the chair. Funds to establish new professorships usually are raised by the hospitals, although they are transferred to the university.

"Raising funds for endowed chairs is an important element of our ongoing development effort," said Allen Peckham, MGH Vice President for Development. "When donors establish professorships, they strengthen the hospital's ability to attract the very best talent in the world of academic medicine."

Occasionally one donor contributes enough to endow a chair. Usually, however, a fund is established by either a major donor or a hospital service and money is raised over several years. Chairs may be named in honor of outstanding physicians (often by grateful patients), the principal donor, or another person or organization.

"An endowed professorship is a great honor for both its namesake and the incumbent, the individual appointed to the chair," said W. Gerald Austen, MD, Chief of the Surgical Service, who is also the Edward D. Churchill Professor of Surgery at HMS.

The newest chairs at MGH are named for two renowned general surgeons — Marshall K. Bartlett, MD, and Claude E. Welch, MD. The new incumbents are international leaders in their fields. A. Benedict Cosimi, MD, the new Welch Professor, is Chief of the MGH Transplantation Unit. Patricia K. Donahoe, MD, is MGH Chief of Pediatric Surgery and the new Bartlett Professor.

The new appointments bring to 30 the MGH staff members who hold endowed chairs at Harvard. At least 11 chairs (some held by faculty at other hospitals) bear the names of MGH leaders.

Dr. Bartlett made important contributions to surgery of the pancreas, liver, and stomach during more than 40 years as a practicing surgeon. He also founded the MGH Surgical Associates, which laid the groundwork for today's full-time academic Surgical Service. After retiring from practice in 1973, he became the first administrative director of the MGH operating rooms. Throughout his career he acted as a mentor to countless young surgeons.

An authority on gastrointestinal disease and cancer, Dr. Welch also is known for his expertise in health care politics and the breadth of his knowledge and experience. He has served as president of such organizations as the Massachusetts Medical Society and the American College of Surgeons and as chairman of the Massachusetts Board of Registration in Medicine. Last fall he published his memoir, *A Twentieth-Century Surgeon: My Life in the Massachusetts General Hospital* (see box on next page).

Dr. Cosimi became Chief of the Transplantation Unit in 1990. His research efforts have focused on controlling transplant rejection and led to the first use of monoclonal antibodies (specialized immune system agents) to supress cells responsible for rejection. Under his direction — and that of his predecessor Paul S. Russell, MD (the John Homans Professor of Surgery at HMS) — the MGH has become one of the country's outstanding transplant centers.

Chief of Pediatric Surgery since 1984, Dr. Donahoe is recognized around the world for contributions to developmental and reproductive biology. She has discovered how certain chemicals control aspects of development in the fetus and how they may inhibit growth of some reproductive system tumors. She and her colleagues pioneered surgical correction of some serious birth defects and instituted innovative, lifesaving treatments for newborns with lung disease. ■

# *Dr. Welch's Book Describes Changes of a Century*

IN HIS BOOK, *A Twentieth-Century Surgeon, My Life in the Massachusetts General Hospital*, Claude E. Welch, MD, chronicles three histories: his own life, from youth in Nebraska to his current position as an elder statesman of surgery; the development of the MGH from a local hospital to one of the world's leading medical and research institutions; and the profound changes that have transformed the practice of surgery over the past 60 years.

(The book is available in the MGH General Store or from Watson Publishing International, PO Box 493, Canton, Ma 02021.)

Dr. Welch began compiling the book from his diaries and notes more than ten years ago. His reminiscences highlight the influences of notable MGH surgeons such as Arthur Allen, MD, and Edward Churchill, MD. Throughout his narration, Dr. Welch puts his personal experiences in context by detailing developments in the greater world of organized medicine and surgery.

Among the subjects to which he devotes chapters are the World War II medical unit staffed by MGH doctors and nurses; efforts to treat cancer, which he calls "the formidable enemy"; changes in medical education and practice; the malpractice crisis; and some of his more unusual operations. In scores of examples and anecdotes, he illustrates his philosophy that, contrary to stereotypes of surgeons as distant and uninvolved with patients, "caring for a sick person is the most important qualification of a surgeon." ■

## *Letter to the Editor*

Dear Editor:

I read with interest the article in *MGH News* (January-February 1993) entitled "In the Best Interest of the Child" in which the activities of the Children and the Law Program are described.

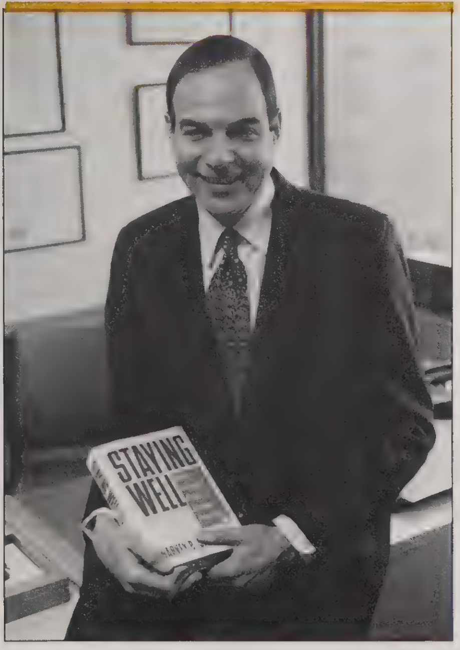
Drs. Ayoub, Herman, Kinscherff, Deutsch and Condie are my respected colleagues, and I applaud the coverage their program has received. Your article failed to mention, however, that the Children and the Law Program, recently arrived at MGH, exists side by side with the Adoption and Custody Unit, which does similar work and has been part of the MGH Child Psychiatry Service since 1980.

The Adoption and Custody Unit consists of two psychologists (Dr. Jenai Wu and Mrs. Elizabeth Geist), two social workers (Miss Ann Daily and Miss Donna Miller), and two child psychiatrists (myself and Dr. Condie, who belongs to both groups). We do a great deal of court related work in divorce and child-neglect cases and are concerned with various aspects of loss in childhood, including bereavement, and various problems that arise in adoptive families. We regularly serve the Suffolk, Middlesex, Norfolk, Barnstable, and Essex Probate Courts, as well as various offices of the Department of Social Services, child placement agencies, and attorneys.

Steven L. Nickman, MD
*Director, Adoption and Custody Unit*
*Child Psychiatry Service*

# Prevention, the Most Important Factor in Staying Well

FOR ALL the wonders of high-technology medicine — the sophisticated diagnostic scanners, intricate surgical techniques, and genetically engineered drugs — it is the simplest of steps that can have the greatest effect in preserving health.



*Dr. Harvey B. Simon*

The power to take those steps does not belong to doctors, nurses, or scientists — it is in the hands of each individual.

In his recently published book Staying Well*: Your Complete Guide to Disease Prevention,* MGH physician Harvey B. Simon, MD, emphasizes the importance of disease prevention and gives his readers detailed information helping them take charge of their own health.

Dr. Simon wrote the book for several reasons. "As a practicing internist for 25 years, I've seen countless people suffer — and some die — from diseases that really could have been prevented. I've emphasized prevention in my practice and have also enjoyed the results of healthy changes in my own life," he said.

In his introduction, Dr. Simon outlines his "Ten Commandments of Prevention" (see box on page 8). The book's second section contains comprehensive discussions of disorders of various bodily systems and describes ways to prevent or lessen their effects.

The final section contains positive recommendations readers can take to enhance health through nutrition, exercise, preventive health care, and avoidance of environmental hazards.

"Preventive efforts can have the most powerful effect on the biggest killers — diseases related to atherosclerosis [the buildup of fatty plaques in arteries] like heart disease and stroke," Dr. Simon said.

"We've already seen great progress there. Deaths from strokes are down 50 percent, and death and disability from heart disease is down 44 percent over the past 40 years. But we still have an enormous way to go."

He added that cancer prevention, something many people despair of, should be an area where future progress is seen. Number one to avoid is smoking — universally accepted as a cause of lung cancer, other malignancies, and heart disease.

Protection against excessive sun

*(Concluded on Page 8)*

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exposure can cut down on skin cancer, the most common of all malignancies. Although some may debate the exact role of diet in cancers of the intestine or breast, the low-fat, high-fiber diet that may cut cancer risks is still sensible to follow.

If prevention is so simple, why are so many people unhealthy? Dr. Simon cites several reasons. For one, people tend to disregard their health as long as they have no problems. In addition, commercial influences make cigarettes, alcohol, and junk foods look attractive.

Even people who try to follow preventive health guidelines may be confused by apparently conflicting reports in the media. "A common lament among my patients is that things seem to change," Dr. Simon said.

"One day they hear that calcium supplements help reduce the risk of osteoporosis; the next day they're told it's not true. Oat bran was a huge fad in the early 1980s and then was abandoned. Now we know that both calcium and oat bran have a role in good health," he noted.

"I tell people to take a long-range view, not to jump on every bit of information that comes along. A diet high in calcium and in fiber is clearly healthful. A lot of attention is paid to little details, but the basic principles are startlingly simple."

The science of preventive medicine may at last be receiving the attention it deserves — as seen in the establishment of treatment and research efforts like the MGH preventive cardiology program (*MGH News*, November 1992). But Dr. Simon emphasizes that the ultimate responsibility for our own health rests with each of us.

"Of course, illness can still occur despite the healthiest of lifestyles. But for most of us it's true that the body we have at age 20 is the body our genes have given us. The body we have at 40, 60, or 80 is the body we've earned." ■

## Dr. Simon's 10 Commandments of Prevention

1. Don't use tobacco or drugs — at all.
2. Don't consume more than two ounces of alcohol per day.
3. Eat a diet low in fat, cholesterol, and salt but high in fiber, fruits, vegetables, and fish.
4. Exercise regularly: one hour each week is helpful, three hours is ideal.
5. Stay lean.
6. Use air bags or wear seat belts, drive prudently, and never drink before you drive.
7. Avoid excessive stress.
8. Minimize your exposure to radiation, ultraviolet rays, chemical pollutants, and other environmental hazards.
9. Protect yourself from sexually transmitted diseases.
10. Obtain regular medical care, including immunizations and screening tests.

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Dr. Warren Zapol

# New Lung Therapy Pioneered at the MGH

Over the past few years a tiny molecule has been causing big excitement in the worlds of biology and medicine. Nitric oxide — a gas long thought to be nothing but a chemical pollutant — has been found to play several critical roles in the body.

It now appears that nitric oxide — not to be confused with nitrous oxide or laughing gas — helps to regulate blood pressure, to defend the body against bacteria and tumor cells, and to transmit messages between nerve cells, perhaps even serving as a critical player in the processes of learning and memory.

Among the scientists around the world who are exploring the newly recognized roles of nitric oxide, a group from the MGH has led the way in investigating the chemical's activity in the lungs. Their discoveries have the potential to save the lives of adults and children affected by serious respiratory disorders.

Warren M. Zapol, MD, an MGH anesthesiologist, has pioneered studies of nitric oxide in the lungs. He explained that in 1987, researchers in England finally identified a mysterious substance they had been searching for — a naturally-occurring chemical, produced by cells lining blood vessels, that relaxed the surrounding muscles and lowered blood pressures. It was nitric oxide.

"As an anesthesiologist who works with and studies the effects of inhaled gases, it seemed natural to study this gas and its effects in the lung," he said. Nitric oxide's action of opening up blood vessels seemed tailor-made for treating several dangerous lung conditions.

The exchange of gases that takes place

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INSIDE

**Eating Disorders Study**
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**A Better Future for Colleen**
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# MGH Researchers Make a Genetic Triple Play

Each human being has some 3 billion pieces of genetic information stored in the DNA. Finding the one piece responsible for a genetic disease is a hugely complex task, requiring endless hours of painstaking, tedious work and more than a little bit of luck.

That makes the accomplishment of the MGH Department of Neurology astounding; during March members of the department reported the discovery of not one but three disease genes.

Teams led by James F. Gusella, PhD, identified the genes for Huntington's disease (HD) and neurofibromatosis Type 2 (NF2). A team led by Robert H. Brown, Jr., MD, PhD, found the gene for amyotrophic lateral sclerosis (ALS), known as Lou Gehrig's disease.

All three successful searches resulted from multi-institutional collaborative efforts. But the ultimate discoveries took place at the MGH Neuroscience Center in Charlestown.

First to be announced was the ALS gene discovery, published in the March 4 issue of the British journal *Nature*. ALS is a degenerative disorder of the brain and spinal cord, which causes weakness and wasting of the muscles.

Patients become paralyzed and eventually die, usually within five years. ALS ended the career of New York Yankee baseball great Lou Gehrig, who died in 1941.

ALS is caused by a defect (mutation) in a gene on chromosome 21 (out of 23 human chromosomes). The gene — discovered by Daniel R. Rosen, PhD, in Dr. Brown's laboratory — carries instructions for an enzyme known as superoxide dismutase (SOD1). The enzyme has been widely studied because it neutralizes dangerous chemicals, called free radicals.

*(Continued on Page 2)*

## EDITORIAL

# A Gamble That Paid Off

IN 1987 THE MGH gambled. It decided to make a huge former warehouse in the Charlestown Navy Yard the site of a massive new research center. The decision meant more than doubling all the research space the hospital had acquired since its founding in 1811. To work, the gamble had to result in finding research support sufficient to fill most of the structure in a few years. That goal has been achieved. With 55 percent of the research money coming from the federal government and the remainder from industry and private foundations, the MGH has raised its annual support for research to $162 million a year. Virtually all of those $162 million are brought annually into the Massachusetts economy, at a time when they are sorely needed. Along with the deployment of those outside dollars, the hospital provides employment to more than 10,000 people, making this institution the largest nongovernment employer in Boston.

The positive effect on the City and State economy, however, is only a beneficial side effect. The purpose of research is to advance medical science. Since Building 149 is a basic research center, it carries out the very kinds of studies which lay the groundwork for the country's continued leadership in biomedical investigation. But basic research takes many years to develop. It is surprising therefore how fast MGH science is reporting major findings.

There is not space here to list all the significant advances in knowledge that have emerged from that one building. Here are a few examples of what world-class scientists brought into a state-of-the-art research center have achieved when given the academic freedom to use their creative talents to explore fundamental mysteries:

They determined how a defective gene often causes a variety of cancers, including breast cancer; produced the first still pictures and — months later — motion pictures showing the brain performing simple tasks; advanced knowledge of the immunology of transplantation; found tantalizing new information about Alzheimer's disease; discovered a master switch which activates part of the body's defense mechanism after such major trauma as a heart attack or car accident. And in 22 days of March madness, they reported the discovery of three long-sought defective genes that cause three different inherited diseases. These feats have astounded the scientific world and have been reported widely on the front pages of America's leading newspapers, as well as highlighted on network television and radio.

Successful research has not brought "profits" to this private, nonprofit hospital. But the outstanding advances have positioned the MGH to continue to attract the best physicians, scientists, and educators to Massachusetts and will, in turn, benefit the City and Commonwealth by bringing new patients to Boston for treatment. And this has come about because its chief executive officer, Dr. J. Robert Buchanan, and the Board of Trustees had the vision and courage to turn an abandoned warehouse in a defunct Navy yard into a world-class house of science at a time when all American hospitals — the MGH included — face an uncertain future. Because of changes brewing in health care, the MGH — like other hospitals — does anticipate difficult times. But if success continues to breed success, Building 149 appears to be at least one outstanding foundation for the future. ■

## — *Triple Play*

*(Continued from Page 1)*

In the body, free radicals attach to other molecules, damaging and detroying cells. When SOD1 functions properly, it latches on or binds to free radicals, keeping them from forming destructive combinations. But the altered form of SOD1 produced in ALS does not protect against free radicals; the mutated enzyme also may be toxic itself.

Dr. Brown explained that they do not yet know whether the altered enzyme is over- or under-activated in ALS. "Whatever the cause, the effect is that when SOD1 is damaged, too many free radicals are set loose," he said.

*Members of the MGH team that discovered the ALS gene: (from left) Jeremiah O'Regan, Peter Sapp, Dr. Daniel Rosen, Dr. Robert Brown.*

Although the gene was discovered at the MGH, Dr. Brown stressed that the

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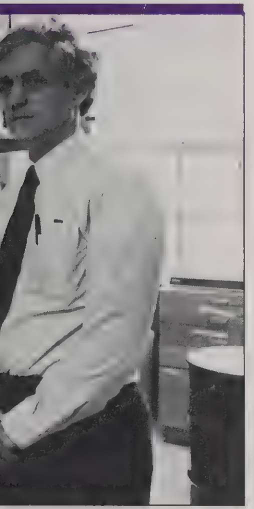
PHOTOGRAPHS: Pages 1,2,3,4,7,8 photographs, Susan McGreevey

project was a multicenter effort. An important Boston collaborator was H. Robert Horvitz, PhD, of the Mass. Institute of Technology.

Identification of the NF2 gene was reported in the March 12 issue of *Cell*. NF2 is a rare, inherited disorder characterized by multiple tumors of the spine and brain. The genetic mechanism that causes NF2 also may be responsible for 30 percent of non-inherited brain tumors.

NF2 is distinct from another inherited illness, neurofibromatosis type 1 (von Recklinghausen's disease), characterized by tumor-like growths on the skin. In the past, NF1 was erroneously confused with the so-called Elephant Man's disease.



The identified gene on chromosome 22 is a tumor supressor gene. Normally it helps prevent cells from growing out of control and forming tumors. Each person carries two copies of a gene, and if both copies of the NF2 gene are damaged, tumors can develop.

The newly identified gene produces a protein that may be a link between the cell membrane, which surrounds each cell, and the cytoskeleton, a complex latticework of filaments that supports the cell.

"This gene suggests a completely different angle on how cells control growth," Dr. Gusella said.

The protein could play a crucial role in such factors as cell shape, movement, division, anchorage, and cell-to-cell communication. More research is needed before investigators know exactly what happens when the protein is inactivated by the observed genetic mutation.

Among members of the team led by Dr. Gusella, were James A. Trofatter, PhD, the paper's first author, and Mia MacCollin, MD.

The discovery of the HD gene — reported in the March 26 issue of *Cell* — was perhaps the month's crowning touch. The gene had been the object of an often frustrating 10-year search by scientists throughout the world.

HD is a progressively debilitating illness that attacks both mind and body by killing brain cells. It begins with small, involuntary movements that gradually spread throughout the body. Later, patients develop psychiatric disturbances and eventually become bedridden. Death is inevitable within 10 to 20 years.

Folksinger Woody Guthrie is among the most famous victims of HD. The disease usually attacks after age 35, and each child of a parent with HD has a 50 percent risk of inheriting the disease.

The search for the HD gene began in 1983 when Dr. Gusella and his colleagues discovered an HD marker — a section of genetic information inherited along with the gene — on chromosome 4. That accomplishment sparked an unusual international collaboration between six groups to find the actual gene responsible for HD.

The goal proved much more elusive than expected, however. While the scientists discovered additional markers that narrowed the area of search, some of the most recent results pointed in two different directions.

Nearing the end of their stamina, the researchers decided to focus on the area where they suspected the gene would lie. Fortunately their suspicion proved correct; the gene for HD was found near the tip of chromosome 4.

The HD gene encodes a protein unlike any seen before. The gene consists of a series of triplets — repeats of the three molecular building blocks that code a particular amino acid (the basic unit of a protein).

In unaffected people the triplet is repeated 11 to 34 times. But in those who inherit HD, the triplet is expanded, repeating from 42 to as many as 86 times.

While it is possible that the number of repeats may correlate with the age of onset of HD, it is much too soon to use this information to make predictions about individual patients.

Marcy MacDonald, PhD, one of the HD researchers, said, "We've crossed a significant threshold, but we've still got a lot of work to do. The next step is to learn more about how this protein functions normally and how it is disrupted in HD." Dr. MacDonald actually found the HD gene, along with two other members of Dr. Gusella's laboratory, Christine M. Ambrose, PhD, and Mabel P. Duyao, PhD.

Learning more about all of these genes may lead to information that can help patients and their families. At this time, however, only the ALS gene discovery points to a possible treatment.

Dr. Brown and his colleagues will be starting trials of therapy with vitamins known to counteract free radicals. Since even vitamins, when taken in large quantities, can be toxic, patients are not advised to try to medicate themselves without the advice of a physician.

Identification of the HD gene will offer a more accurate screening test for the disease, although whether or not to be screened remains a highly-charged decision for those at risk, one which requires sensitive genetic counseling.

But the real promise for those affected by any of these illnesses is that better understanding of how the genetic defect leads to the disease's effects will ultimately lead to ways to treat or even prevent these devastating illnesses. ■

*Both the HD gene and the NF2 gene were discovered in the laboratory of Dr. James Gusella. Team leaders pictured are (from left) Drs. James Trofatter, Marcy MacDonald, Mia MacCollin, James Gusella, Mabel Duyao, and Christine Ambrose.*

(Continued from Page 1)

in the lung depends on a network of tiny blood vessels in close contact with millions of air sacs. Blood that is depleted of oxygen travels from the heart into this network. There oxygen passes from the air into the blood, and carbon dioxide is released to be exhaled.

There are several conditions in which this process is disrupted. The blood vessels can become constricted, preventing enough blood from entering the lung; air sacs can fill with fluid or debris, restricting the supply of air. The result is insufficient oxygen in the bloodstream and a buildup of carbon dioxide and other waste products.

Medications that can open up or dilate blood vessels exist, but they have a significant drawback. They are injected intravenously and travel throughout the body, causing an overall drop in blood pressure that can lead to shock.

The exciting thing about nitric oxide, Dr. Zapol explained, is that it can be inhaled into the lung. When it comes into contact with hemoglobin (the oxygen-carrying component of blood), nitric oxide is immediately inactivated; thus the blood-vessel-relaxing effect is confined to the lungs.

Several steps had to be taken before nitric oxide could be tested for its effect upon human disease. Dr. Zapol and one of his fellows — Claes Frostell, MD, PhD — devised a system to administer the gas continuously without allowing the formation of its highly poisonous byproduct, nitrogen dioxide. Then the researchers had to conduct animal studies to confirm that nitric oxide itself would work without causing damaging side effects.

In their first animal studies, they administered low levels of nitric oxide to sheep and found that nothing happened. They realized that in normal animals, where the lung's vessels are dilated, nitric oxide had no effect. So they tried again after giving the sheep a drug that would constrict blood vessels in the lung.

***"We found that nitric oxide was a dream!" Dr. Zapol said. "It would selectively dilate blood vessels in the lung but wouldn't dilate those in the rest of the body. This was something we'd been seeking for more than 20 years."***

They followed up this test with more animal studies. One demonstrated nitric oxide's ability to reduce contraction in response to low oxygen levels in the air, a more natural situation than the drug-induced contraction of the earlier tests. In another, the animals breathed the nitric oxide mixture for prolonged periods of time to make sure there was no damage to their lungs.

"Once we knew nitric oxide worked the way we expected and that it appeared to be safe, we were ready to try it in people," Dr. Zapol said.

The first of these studies tested nitric oxide in a rare, potentially fatal disease of infants, persistent pulmonary hypertension of the newborn (PPHN). Jesse D. Roberts, MD, an MGH neonatologist and anesthesiologist, led the study in cooperation with Dr. Zapol's team.

"A baby doesn't use its lungs before it is born, so blood flow to the lungs is very limited in the fetus," Dr. Roberts explained. "In the first four to five minutes of life, blood flow to the lungs usually increases ten-fold. In PPNH, for some reason, this increase does not occur. The lung's vessels remain in a contracted, pre-birth state. The babies breathe, but they can't get enough oxygen and turn blue."

Treatment for PPHN includes administering high levels of oxygen, drugs that relax blood vessels, and use of ventilators. But those techniques all have risks and often they do not work. A sophisticated technique called ECMO (extracorporeal membrane oxygenation), partially developed at the MGH (*MGH News*, November 1975), is effective. But it is expensive, has its own risks, and is available only in major medical centers.

Six babies brought to the MGH for PPHN were the first to be treated with nitric oxide. They were the sickest of the sick, those for whom the standard therapies had not worked; ECMO appeared to be their last chance. First, however, Dr. Roberts had them breathe the nitric oxide mixture for about 30 minutes.

*Dr. Jesse Roberts*

In all of the babies, nitric oxide improved the level of oxygen in their blood. One baby remained pink (a sign that the blood has enough oxygen) after brief exposure to nitric oxide and recovered rapidly.

While four of the other babies required ECMO after the nitric oxide treatment, they also eventually recovered. The last baby could not be put on ECMO because he had already undergone two futile rounds of the therapy. He continued to inhale nitric oxide for a month but died of other complications.

"During that entire month, there was no evidence of any damage to the baby's lungs from nitric oxide," Dr. Roberts noted.

Drs. Roberts and Zapol are following up these first, preliminary results in a larger study with five hospitals across the country. "We want to determine, among other things, when nitric oxide should be used," Dr. Roberts said. "Right now, because the treatment is so new, we're waiting until babies are very sick. If nitric oxide proves less toxic than conventional therapies, it may be given to babies as soon as they develop PPHN."

Dr. Roberts and his colleagues — Drs. Peter Lang in cardiology and Gus Vlahakes in cardiac surgery — also found that nitric oxide appears useful in treating babies with congenital (inborn) heart defects. In these babies, increased pressures often develop in the lung's blood vessels. The pressure can reduce oxygen uptake and ultimately damage both the lung and the heart.

In the first study of ten babies, the doctors showed that breathing nitric oxide can reduce these pressures. In the future, infants with some congenital heart defects may inhale nitric oxide to prevent increased lung blood pressures. This would allow the babies to become stronger and grow more quickly. Corrective surgery that may be necessary could then be put off until they are older.

At the same time as Dr. Roberts was pursuing pediatric uses for nitric oxide, Dr. Zapol and his team were investigating the gas's use to treat a condition called adult respiratory distress syndrome (ARDS). In ARDS, parts of the lung fill up with fluid and debris, cutting off gas exchange. The condition — caused by traumatic injury or by an infection such as pneumonia — can lead to a rapid death.

There is a critical difference between ARDS and PPHN. Blood vessels throughout the lung are contracted in PPHN. But in ARDS parts of the lung are clogged and parts are open.

"In the normal lung, ventilation [the flow of air] matches perfusion [the flow of blood]," Dr. Zapol explained. "In ARDS, part of the lung doesn't function. Blood that travels to that area doesn't come into contact with any oxygen and remains blue. You wouldn't want to increase the blood flow to that part of the lung, but you would want to maximize blood flow to the areas that are clear."

Nitric oxide seemed ideal. As a gas, it should be carried only to those areas of the lung where air flow was maintained. There it would open only the adjacent blood vessels, matching ventilation with perfusion as in the healthy lung.

The first tests of nitric oxide in ARDS were conducted by a team of German doctors led by a former MGH colleague of Dr. Zapol's, Konrad J. Falke, MD. Dr. Zapol also collaborated with the German group.

At his hospital in Berlin, Dr. Falke, who trained at the MGH, has access to a sophisticated monitoring technique called MIGET (multiple inert gas elimination technique). This procedure gives detailed readings of how well a patient's lungs function.

"We've actually been using nitric oxide for years, but we never knew it."

The patients in the German study inhaled nitric oxide for as long as they needed it — from less than a day to more than a month. The therapy immediately reduced pressures in the pulmonary artery (which brings blood from the heart to the lungs) and improved oxygen levels in the blood. The MIGET study confirmed that, as hoped, nitric oxide improved blood flow in the ventilated regions of the lung but not in the damaged, fluid-filled areas.

"Nitric oxide is able to make the lungs 'smarter,' more efficient," said Dr. Zapol. "As a result, we were able to reduce the level of oxygen administered by 15 percent. That's very important because high levels of oxygen can further damage the lung."

The researchers also compared nitric oxide to prostacyclin, an intravenous drug which relaxes blood vessels. During the short time that patients were on prostacyclin, blood flow increased to the entire lung, including the diseased areas, causing a drop in blood oxygen levels.

The German team and Dr. Zapol were the first to publish their results with nitric oxide, largely because of the advantage received from MIGET. The technique allowed rapid measurements of results of the MGH-developed therapy. But the MGH team has found similar results in parallel studies of intensive care patients.

"You know," Dr. Zapol said, "we've actually been using nitric oxide for years, but we never knew it. The nitroglycerine tablets that people with heart disease take to relieve angina [chest pain] are now known to release nitric oxide in the body."

Part of the beauty of nitric oxide is that it is a natural substance that is being replaced in the body. Evidence is growing that PPHN actually results from a lack of natural nitric oxide production.

Of course, there are still questions to be resolved, particularly whether nitric oxide treatment has any toxic effects. Its long-time reputation as a pollutant — it can be found in exhaust fumes and cigarette smoke — requires caution before it can be adopted as a regular therapy. So far, however, no one has found evidence of any toxicity at the low levels required to produce the benefits seen.

In the meantime, the positive results seen in these first MGH pulmonary studies have sparked new research into respiratory uses for nitric oxide here and elsewhere.

In addition to PPHN and ARDS, the gas holds promise for treating other conditions that raise blood pressures in the lung — including primary pulmonary hypertension and emphysema. It could possibly help patients recovering from heart surgery and lung transplants and appears to be effective in reducing the spasms of the bronchial muscles that occur in asthma.

"Nitric oxide was overlooked for years because it was so simple," Dr. Zapol said. "While we still have questions to answer, I think it's going to prove to be very useful, and that someday every delivery room and intensive care unit will have a supply of nitric oxide on hand. It's an inexpensive therapy, it seems to be less toxic than the treatments we're using now, and when it works, it works spectacularly well." ■

# Study Takes Long-Term Look at Eating Disorders

DO PEOPLE ever recover from eating disorders? Despite several decades of increased awareness of and attention to these conditions, there is still no clear answer to that question.

Now researchers at the MGH have embarked on the first large-scale study aimed at answering that question and clarifying related issues, such as which patients have a greater risk of relapsing? What is the long-term outlook for patients with eating disorders? Can eating disorders eventually "burn out" by themselves?

David B. Herzog, MD, director of the MGH Eating Disorders Unit, is the leader of the five-year study which is following more than 200 individuals with anorexia nervosa, bulimia nervosa, or a combination of both conditions.

Both types of disorder are most commonly seen in young women. Those with anorexia seek to rigidly control their weight by such means as radically restricting food, purging calories through vomiting or the use of laxatives, and obsessive exercising.

At the same time as their weight drops to unhealthy, even dangerous levels, they continue to see themselves as overweight, always needing to lose "just a few more pounds."

People with bulimia can be normal weight, overweight, or underweight. They binge on huge amounts of food and then seek to relieve themselves of the calories — and their feelings of guilt and shame — by the sort of purging techniques described above.

While anorexics rarely recognize that they have a problem, bulimics are profoundly embarrassed by their actions and their sense of being out of control. They usually eat and purge in secret.

All participants in the MGH study came at some time to the Eating Disorders Unit for evaluation. Some have been treated at the unit; some treated elsewhere; others did not choose to receive any therapy.

Every three months, participants are extensively interviewed about their eating practices and current psychological state — thoughts and feelings that may contribute to their disorder. The researchers hope to find correlations between specific aspects of eating disorders, any accompanying problems, and the incidence of recovery or relapse.

The study is now in its fourth year, and preliminary results, based on material gathered in the first 18 months, will be published later this year. The research has produced some interesting observations, although it is too soon to say whether they will hold up over time.

In general, the great majority of bulimic patients showed improvement — that is, they substantially reduced their disordered eating behavior — as did about half the anorexic patients. While 60 percent of the bulimic patients were totally free of eating disorder symptoms, only 10 percent of anorexics were totally symptom-free.

Anorexics who were able to reduce their symptoms, however, were able to sustain that improvement. In contrast, bulimics who improved were more likely to relapse.

"The evidence suggests that it may be important to achieve the asymptomatic [without any symptoms] state in the bulimic population to avoid relapse," Dr. Herzog explained. "In the anorexics, it looks like it may be helpful to just reduce the level of their symptoms, to get them out of the deepest hole of anorexia, since they don't seem to fall back in as readily."

Achieving that reduction of symptoms in anorexia is not easy, however. Getting a patient to acknowledge the problem can be a major hurdle. Treatments for anorexia can include both individual and family psychotherapy, as well as intensive nutritional counseling and keeping a close watch on the medical problems that accompany self-starvation.

Despite instances of successful treatment of patients with anorexia, no particularly therapy has been shown to be consistently effective in the disorder.

The ability to determine the best therapy for each patient could make a critical difference, Dr. Herzog noted, because anorexic patients have a real risk of dying from the physical and psychological effects of their disorder. Some studies have indicated that from 5 to 15 percent of anorexics may die from their disorder.

The treatment outlook for bulimia is considerably more optimistic. Several types of psychotherapy have been helpful, and certain antidepressant medications also appear useful (*MGH News,* June 1990).

Dr. Herzog hopes that future results from the study (which may be extended for another five years) will help sort out the role of treatment strategies, as well as clarify the impact of psychological problems that accompany eating disorders.

In the case of both anorexia and bulimia, Dr. Herzog noted, the issue of "recovery" is more complicated than reducing or eliminating food-related symptoms. Some who have resumed normal eating behaviors still hold abnormal attitudes about food. Others may exchange eating disorders for other compulsive behaviors.

Problems with low self-esteem and basic elements of personality that can contribute to eating disorders — perfectionism among anorexics, impulsiveness in bulimics — remain and may need to be addressed in continuing counseling. (See sidebar for a patient's viewpoint on recovery.)

Dr. Herzog compared eating disorders to other addictions by which people try to shield themselves from feelings of depression or inadequacy. "Young women experiencing emotional distress may adopt certain behaviors — not necessarily consciously — in order to function in the world," he said

"The fact that so many young women choose this way to assert some control over their lives certainly reflects an excessive emphasis on thinness in this culture. But that's only one part of the picture. We also need to find ways to help young people feel respected for who they are and achieve healthy relationships with family and friends." ■

## A Patient's Perspective on Recovery

Boston Phoenix *reporter Caroline Knapp, a patient of Dr. Herzog's, struggled with anorexia for four years. The following is an excerpt from an article she wrote reflecting on the process of recovering from an eating disorder.* [Editor's note]

At some point eating — an act that had caused profound anxiety in the past — simply ceased to be such a big deal. I ate when I was hungry, I stopped when I was full. My weight leveled off to a point where my body seemed to want it to be . . . .

But to say that I "recovered" during that time applies primarily to the clinical side of things. And to say that the more complicated, internal struggles vanished along with the preoccupation — the daily battles with things like closeness and vulnerability and anger — would be a lie.

The therapist who helped get me on the right road has this perspective on addictions: "It's very hard to give something up unless you have something to replace it with." Indeed. Am I rigid and ritualistic about food these days? No. But am I rigid about other things? Exercise? Work? My daily routines? Absolutely. . . .

So have I "recovered"? To the extent that I no longer starve myself, absolutely. And to the extent that I've been able to apply a lot of the lessons I learned (albeit indirectly) from food to some of the more gratifying areas of life, again, I'd say yes. Learning to feel hunger and fullness again, for example, are the first steps toward learning to feel the other things that humans need to feel: anger, sadness, love, affection.

Still, the word "recovery" implies some kind of final break with a past behavior or past personality. Anorexia is no longer what I am, but it is — and I believe I say this with acceptance, rather than regret — a part of who I am.

*Excerpted with permission from the* Boston Phoenix.

# Search for Answers Leads to a Better Future for Colleen

A mother's determination to find out about her daughter's birth defect, a young doctor's willingness to dig out the answers, and the skills of a neurosurgeon: all these factors came together last fall to improve — and possibly save — the life of a little New Hampshire girl.

Colleen Dionne was born with achondroplasia, the most common form of a group of conditions called skeletal dysplasia (malformations of the bones or cartilage). Children with achondroplasia have very short arms and legs. Their heads appear larger than normal, and they may have a variety of physical problems related to abnormal bone growth. Achondroplasia has no effect on intelligence.

***Colleen's mother Diane Dionne set out to learn all she could about the condition. "My biggest concern was that — in the future — I didn't want to find out too late that there was something we could have done to prevent a problem for Colleen," she said.***

***Ms. Dionne pursued several sources of information and eventually was directed to Lewis Holmes, MD, MGH head of embryology and teratology (fetal growth and birth defects).***

At that time, Joan Stoler, MD, was completing a genetics fellowship under Dr. Holmes and had recently presented a talk on skeletal dysplasias — including achondroplasia — at a departmental seminar. When Colleen's mother made an appointment to bring her in, Dr. Holmes suggested that Dr. Stoler join in the consultation.

Colleen was eight months old when Dr. Stoler first saw her. Although she had made some developmental progress, her arms and legs were "floppy" — indicating a lack of normal muscular strength and control — and she had trouble holding up her head. The symptoms indicated a possible neurological problem.

*Colleen Dionne, now able to stand at 18 months old.*

In preparing for her presentation, Dr. Stoler had read studies by Dr. Richard Pauli of the University of Wisconsin, involving about 50 children with achondroplasia. His work looked at the possible effects of bone malformations on the

*(Concluded on Page 8)*

## — Colleen

*(Concluded from Page 7)*

upper spinal cord — particularly focusing on the opening at the base of the skull (the foramen magnum), through which the cord passes.

Children with achondroplasia typically have a smaller-than-normal foramen. But if the opening were so small that the spinal cord was pinched or squeezed, there could be serious neurological consequences.

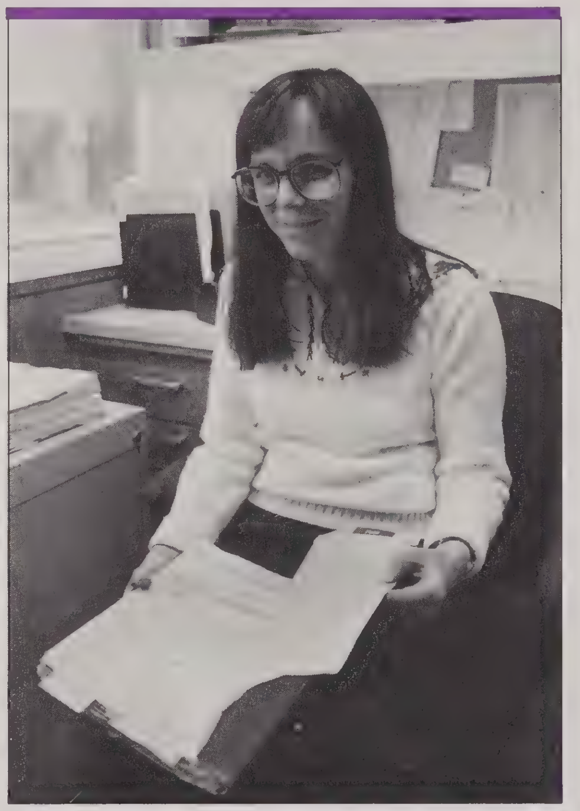
Dr. Pauli had made recommendations in the medical literature about screening children with achondroplasia for problems with foramen size and had compiled measurements from his own research group. His work indicated that those children whose measurements were below average in two dimensions were at risk for spinal cord damage.

Dr. Stoler consulted with Dr. Pauli about Colleen and reviewed the information from his studies. She ordered a CT scan, which showed that Colleen's foramen was a little below average in one measurement and significantly below average in another.

"The question then was what do we do?" Dr. Stoler said. "We ran several additional studies on her, which were normal except for changes that would be expected for achondroplasia. But when we ran the MRI [magnetic resonance imaging study], it showed that she had very significant cord compression."

On the basis of this information, Colleen was referred to Paul Chapman, MD, an MGH neurosurgeon who performed an operation to enlarge the foramen by removing bone from the back of the opening. He noted that the compression on Colleen's spinal cord could have led to very serious problems.

"She would have been at significant risk for progressive weakness in her arms and legs and for breathing difficulties that could have been life threatening," Dr. Chapman said.



*Dr. Joan Stoler*

After the surgery — done when Colleen was 15 months old — she showed dramatic progress. Before the operation she was unable to sit up, her legs were significantly weaker than her arms, and she still had problems controlling her head.

Three months later, Colleen was sitting up, crawling, climbing, and pulling herself up to stand. "The changes are incredible," said her mother. "She's well on her way to getting ready to walk."

Dr. Stoler will continue to follow Colleen to watch for other difficulties related to her disorder; she may eventually need surgery on her lower back or legs. But no problems are anticipated that would put her at the sort of serious risk posed by upper spinal cord compression.

"In the future, I'd like to look into issues related to screening these children," Dr. Stoler says. "Dr. Pauli's work is regarded as somewhat controversial, and we need to have studies with larger groups of children to resolve whether or not we should run tests on every child with achondroplasia or if there are other ways to find out who may be at risk."

Said Colleen's mother, "Dr. Stoler is a perfect example of one of the qualities of a good doctor, as defined by the Little People of America [an advocacy group for people with short stature].

"She wasn't afraid to say, 'I don't know, but I'll find out.' She didn't hesitate to consult with others to find the right information to help Colleen. I can't speak highly enough of her and everyone else at the MGH." ■

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News

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# New Technique Helps Restore the Ability to Swallow

THINK for a moment about swallowing. The process that seems so automatic involves a delicate interplay of muscles in the mouth, throat, and esophagus. While one can consciously control the timing of a swallow, few could actually describe what they do when they swallow.

So what can be done when the process of swallowing goes wrong? A surprisingly large number of people — estimated to be as many as 10 million in this country — experience swallowing difficulty or dysphagia as the result of damage to the nervous system or to the structures involved in swallowing. This can lead to problems with malnutrition, social isolation, and lung disease.

Helping patients with dysphagia — which is often the result of a stroke or cancer — is one responsibility of speech-language pathologists. A member of the MGH Speech-Language Pathology Department has introduced a technique that can significantly reduce the time involved in regaining the ability to swallow. It also assists in restoring function to patients who previously had little hope of recovery and has the potential for reducing the costs of therapy.

Maggie Lee Huckabee, MA, CCC/SLP, senior speech-language pathologist, began employing biofeedback in swallowing treatment four years ago, while she was working at a rehabilitation center in Texas. Biofeedback produces a visible display of usually unconscious bodily functions — such as blood pressure, heartbeat, or body temperature — to help patients gain some control over that function.

Ms. Huckabee had a patient who had

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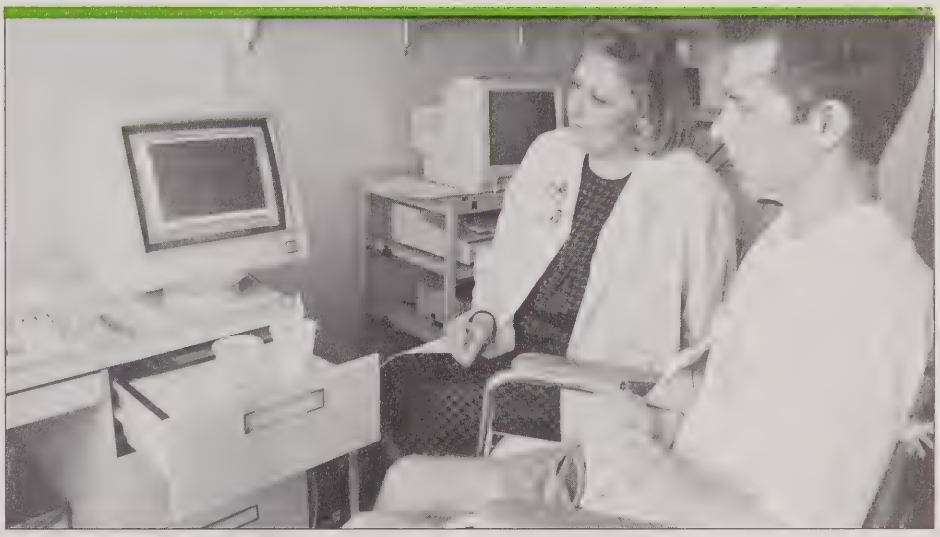

*Speech-language pathologist Maggie Lee Huckabee takes patient Bruce Alves through a series of swallowing exercises. A biofeedback machine detects signals generated by muscles under Mr. Alves' chin and displays them as a visual pattern on a computer screen.*

## *Specialists Pool Efforts to Relieve Pain*

IF THERE is one experience shared by large numbers of patients in any hospital, it is pain. For some, pain is transient, the result of an injury or operation from which they soon heal. For others, the pain of an injury or disease can become a long-term, even permanent presence in their lives.

The MGH has long been a leader in the battle against pain, and several of today's latest techniques for pain management were developed in part here. Now the hospital has established a comprehensive, interdepartmental pain center to help bring improved pain relief to both inpatients and outpatients.

The MGH Pain Center is the result of a merger between the Department of Anesthesia's Pain Service and the Department of Neurology's Cancer Pain Service. While members of these departments staff the center, its activities rely on close collaborative relationships with specialists in many areas.

"We are a multidisciplinary group and interact closely with colleagues in such areas as behavioral medicine, neuro-

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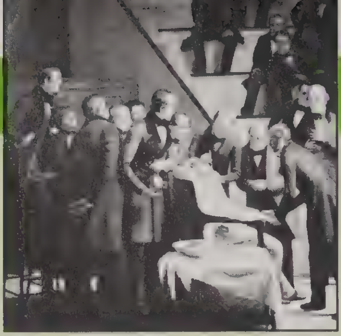
EDITORIAL



# Reforming Health Care

Her patient was only 40 years old. Too young to be doomed to a life of artificial feeding. Too young to risk death from choking on saliva she is unable to swallow—or to die of aspiration pneumonia. So the caretaker, now a senior speech-language pathologist at the MGH, innovated. She developed a better method of teaching the millions of Americans who lose the ability to swallow (perhaps because of a stroke or cancer) how to relearn what the fortunate rest of us have always taken for granted.

Speech-language pathologists are not physicians. In patient care settings they hold master's degrees, rarely doctorates. They represent just one of the many allied health specialties that work with doctors to heal the sick.

* * *

An often deranged homeless patient who frequently became disruptive was unwanted at the shelter where he slept. His two MGH physicians labored for months to address his physical and psychological problems. For reasons largely beyond his control, he was a difficult patient who irregularly took his medications and often failed to keep his appointments. He regularly complained about the very physicians who spent long hours with him and went out of their way to be patient with him. His situation at his shelter became untenable, and he wanted to leave it before he was forced to.

His physicians worked with an MGH social worker to find him more suitable housing. The State too had tried but failed because appropriate accommodations are scarce and hardly any organization wanted to house this unfortunate man. After an intensive and painstaking search, the social worker identified several places which were entirely suitable, surprisingly good, and which would accept him.

What makes the speech-language pathologist, the social worker, and the physicians special is their training, intelligence, creativity, compassion, and dedication. None of the professionals mentioned, including the physician-specialists, command high salaries. The young doctors are many years away from, and may never reach, the national average incomes one reads about for specialists. (In fact it is not generally realized that many world-famous MGH doctors earn less than colleagues who work in suburban communities.) ***Special hospitals like the MGH are replete with such specialists as the speech-language pathologist, the social worker, and the physicians. At the MGH these special caretakers permeate the organization. Let's hope that in the zeal to reform health care the nation's leaders do not homogenize or even destroy these special hospitals.*** ■

## —*Ability to Swallow*

*(Continued from Page 1)*

undergone considerable surgery and radiation therapy on her mouth and neck for oral cancer and, as a result, had serious difficulty speaking and swallowing. "I really was afraid she'd never be able to swallow again. But she was only 40 years old, so I decided to try something new," she said.

The something new was an EMG (electromyography) biofeedback machine, which displays a pattern reflecting the electric current produced by a contracting muscle. While speech-language pathologists had been using EMG biofeedback to treat other conditions, such as stuttering, Ms. Huckabee appears to be the first to use the technique in swallowing treatment.

Placing the EMG electrodes (which pick up electrical impulses) right under the chin measures the activity of several muscles involved in swallowing. The patterns generated provide a visible representation of muscle movement during swallowing treatment exercises. This is proving invaluable to both speech pathologist and patient.

"Before, I might ask a patient to swallow hard and hold the Adam's apple [larynx or voice box] up high for several seconds," explained Ms. Huckabee, who came to the MGH last summer. "But all I could do was watch and say, 'Well it *looks* like that's what you did.' I could never know for sure."

The patterns produced by the biofeedback machine, on the other hand, are an objective measure of what is actually happening with the patient's muscles.

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PHOTOGRAPHS: All photos by Susan McGreevey. Illustrations page 3 courtesy of Maggie Lee Huckabee.

Measurements over time can track a patient's progress and can be compared with the characteristic patterns of a normal swallow.

For the patient, learning how to control and change the biofeedback pattern provides a visible, concrete goal to strive for. And it can help improve awareness of the process of swallowing.

Kenneth Gould, a 76-year-old man from Pittsburgh, was treated at the MGH during March. He said, "When you're on the biofeedback machine, you know what it felt like and looked like when the therapist says you made a good swallow. And when you make a bad one, the machine reflects that immediately."

The ability to "make a good swallow" is of obvious importance in eating. But there are less obvious consequences of dysphagia that can be quite serious.

Normal secretions of saliva may choke someone who cannot swallow. If a dysphagic patient tries to eat or drink, some food or liquid may stay in the throat and eventually be inhaled (aspirated) into the lungs. This can lead to aspiration pneumonia, which can be life-threatening.

Mr. Gould was one of those who developed pneumonia. His dysphagia resulted from complications of cardiac surgery at his local hospital. After the pneumonia, he received nourishment through a tube that passed directly into his stomach.

While he disliked not being able to take food by mouth, his experience with pneumonia made the prospect of eating rather daunting.

His wife, Mary Anne Gould, said, "He wouldn't admit it, but I knew he had a certain amount of hesitancy about trying to eat again. The therapists Maggie and Tessa [Goldsmith] were very positive and reassuring. They really built his confidence."

With the reinforcement provided by the biofeedback, Mr. Gould was able to make remarkable progress in a week of outpatient treatment at the MGH. On the second day of therapy, he swallowed his first food in seven months.

"I wish I'd had a camera to record the look on his face when he took that first swallow of applesauce," Mrs. Gould said.

Since his return home, Mr. Gould is continuing with twice-weekly swallowing treatment and is able to eat soft foods like scrambled eggs or canned fruit.

"It's pretty easy for some expert to tell you 'how' to swallow, but that really doesn't help someone like me," he said. "You need something you can see or hear or feel, something that will give you direction. When I have a target, I'll work toward it."

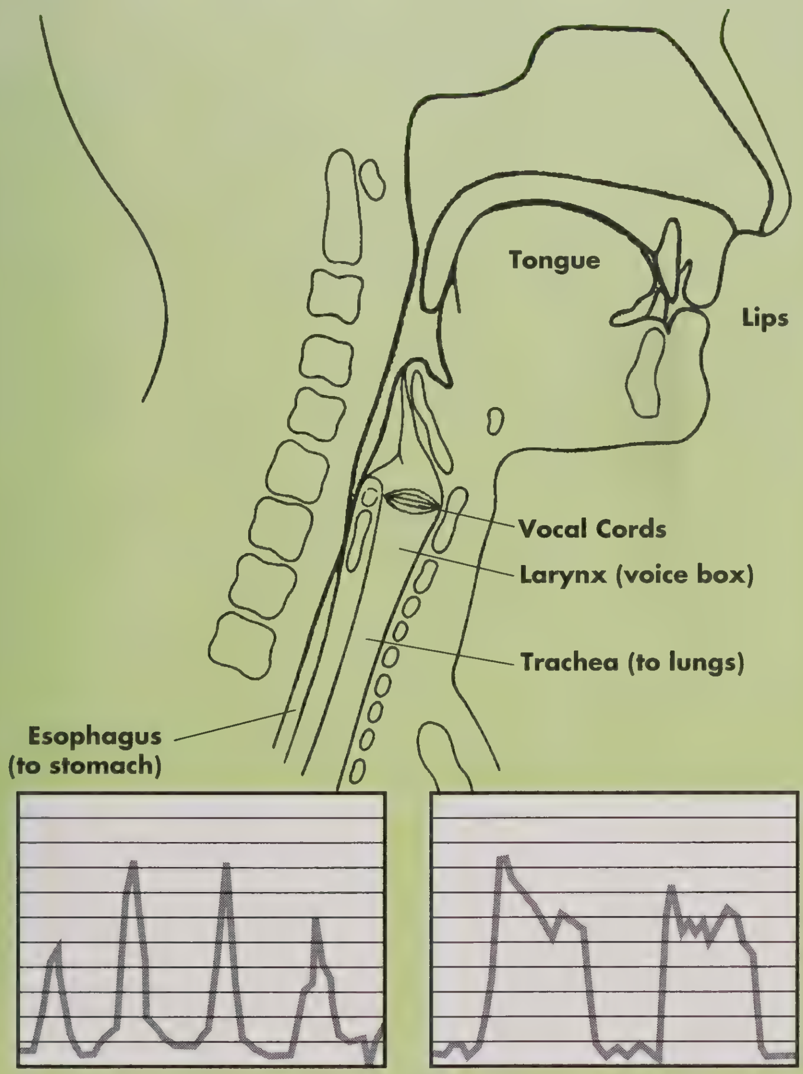
Mr. Gould's experience points up the great time savings that can be achieved with the biofeedback technique: he made more progress in one week of treatment at the MGH than he had in months of conventional therapy. Achieving results quickly provides a powerful incentive for the patient and also helps in the ever-present effort to keep costs low.

"This enables the speech pathologist to be more effective and efficient," said Julie Atwood, director of the MGH Speech-Language Pathology Department. "We must be as efficient as possible because insurers aren't going to pay for six months of treatment."

Building on the successful introduction of EMG biofeedback, MGH speech-language pathologists have developed — in cooperation with hospital dietitians, social workers, and physicians — the Outpatient Accelerated Swallowing Program. This interdisciplinary effort provides dysphagic patients with a comprehensive, one-week program of diagnosis and aggressive treatment.

Outside interest also has been growing in the technique, based on several articles published by Ms. Huckabee, and the department recently sponsored a swallowing conference for speech pathologists from throughout New England.

"I think many of them will go back to their institutions and borrow, buy, or rent an EMG machine to start a program based on Maggie's work," said Ms. Atwood. ■



*Biofeedback patterns of a patient with swallowing problems (dysphagia) early in treatment (left) and after several sessions of therapy (right). The boxlike shape of the line on the right is more typical of a normal swallow.*

# — Efforts to Relieve Pain

*(Continued from Page 1)*

surgery, orthopedics, oral surgery, physical therapy, and the pain rehabilitation service at Spaulding Rehabilitation Hospital," said Daniel B. Carr, MD, director of the MGH Pain Center. "Providing the best patient care also requires working with staff from nursing, psychiatry, pharmacy, and social service."

***Representatives from these areas meet twice a week to discuss the needs of specific patients and how their individual specialties can contribute to optimal care.***

*Dr. Alyssa Lebel (left) and Annabel Edwards, RN, check Rita Linder's patient-controlled analgesia unit. Ms. Linder can control the administration of pain-killing medication by pressing the button she holds in her hand.*

While the center provides services for patients with all types of pain, activities are organized around three focal areas: acute pain, cancer pain, and chronic pain. Dr. Carr, who is an anesthesiologist and internist, noted that the emphasis for each area is the same: providing maximum pain relief, improved function, and the best possible overall quality of life in accord with the preferences of each patient.

Alyssa Lebel, MD, a pediatric neurologist in the center, explained, "A big part of our job is education — of patients, families, and other health care professionals — about the kinds of therapies we can offer today."

Several therapies regarded as revolutionary when first introduced at the MGH and other leading hospitals are now becoming accepted as routine treatment. One of these is PCA — patient controlled analgesia (*MGH News*, October 1988).

This technique allows patients to administer pain-killing drugs like morphine to themselves through an intravenous tube by means of a special battery-operated pump. When patients become uncomfortable, they can self-administer a dose of medication by pressing a hand-held button.

Although the pump is programmed to prevent an excessive dose, patients on PCA usually use less medication than patients who receive periodic shots either on a set schedule or upon request. The pump also can be set to deliver a constant, low-level dose of medication.

"Until about a half dozen years ago, treatment of acute pain — pain from an accident or injury — hadn't changed much since World War I," said J. Bucknam McPeek, MD, director of the acute pain service in the pain center. "The process produced periods of relative overdose, when patients felt groggy, and underdose, during which they suffered pain.

"With the new methods that have come into widespread use here at the MGH, many patients now report they have little or no pain during their hospital stay," he added.

Proper treatment for patients with acute pain does more than keep them comfortable. It can actually speed recovery and prevent possible complications that may cause pain to persist.

Annabel Edwards, RN, CNS, clinical nurse specialist in the new MGH Pain Center, recalled that before current pain management concepts became accepted, pain could severely restrict important activities of patients after surgery.

"It was hard for patients who were hurting to get up and move around," she said. "We had to cajole them to walk and do other things that help prevent problems like pneumonia. The evidence is getting stronger that aggressive pain management leads to better patient outcomes."

That principle was supported last year by a federal panel, cochaired by Dr. Carr, that issued guidelines for acute pain treatment under the sponsorship of the US Department of Health and Human Services. Their recommendations, based on a two-year investigation of current practices, refuted several myths about pain.

Indeed it is now becoming clear that preventing pain from the very beginning can avoid some cases of chronic pain. Pain center neurologist David Borsook, MD, PhD, explained that some pain can cause permanent changes in the nervous system.

"When a nerve is cut or damaged," he said, "it sends messages to the central nervous system [brain and spinal cord]. If a lot of these messages are sent, it causes the release of what are called excitatory amino acids. And this release, in excess, can kill neurons [nerve cells] in the central nervous system."

This mechanism is believed to lie behind the "phantom pains" felt by patients who have had an amputation. Similar pain may be generated from operations that involve severing large portions of nerve — including removing some tumors.

"It now appears that preemptive analgesia — starting patients on pain medication before surgery — can essentially dampen down the nervous system and prevent surgical trauma from causing permanent changes in the nervous system," Dr. Borsook said.

While preventing chronic pain from developing is a goal for the future, helping patients with chronic pain lead better lives is a reality today. Standard pain-relieving medications have a role for these patients, but other categories of drugs — used for treating depression, anxiety, and seizure disorders — have also proven useful.

"These medications can affect the release of pain modulators and neurotransmitters [chemicals that carry signals between nerve cells]," Dr. Lebel said.

"They reset the balance of the nervous system in an effort to inhibit pain."

The impact of chronic pain on patient's lives can be devastating — affecting their ability to work, their family relationships, their overall self-esteem. The pain center's multidisciplinary team brings in specialists from several areas that offer nondrug-based approaches to help patients cope.

David Ahern, PhD, Director of the Behavioral Medicine Unit in the Department of Psychiatry, explained that his group collaborates in evaluating and designing integrated treatments for patients, with a focus on the effect pain has on their lives, their emotions, and their families. "Our primary goal is to help patients lead lives that are more normal, more satisfying, despite any pain that may persist," he said.

Among therapeutic approaches offered by behavioral medicine are progressive muscle relaxation, biofeedback, distraction techniques (directing patients' attention away from pain), and behavior modification. Supportive counseling for patients and families can address emotional issues and help identify changes in the home environment that encourage patients to be more active.

*Physical therapist Harriet Wittink encourages Michele DePippo through her exercise routine. Exercise can help chronic pain patients become more active and better manage their pain.*

Physical and occupational therapy handle these issues from their own specialized approach. Physical therapist Harriet Wittink, MS,PT,OCS, explained that patients with chronic back pain, for example, often are impaired on two levels.

"They have initial impairment from their injury and secondary impairments from what is called deconditioning syndrome. This is the result of months, sometimes years, of inactivity, which translates into decreased range of motion, decreased strength and endurance, decreased ability to do any kind of activity," she said.

To help patients recover from the effects of inactivity and restore their functional capacity, Ms. Wittink and her colleagues devise exercise programs they can follow at home. Patients are also encouraged to use heat, cold and other nondrug techniques to manage their pain on their own.

"We make them responsible for part of their own therapy," Ms. Wittink explained. "And when they see the progress they can make, increasing repetitions of an exercise and improving their flexibility, they feel they have more control over their pain."

In fact, she added, while the exercises are targeted to improving fitness and flexibility, most patients find their experience of pain decreases as their ability to function improves.

Many people believe that pain associated with cancer — especially cancer that cannot be cured — is unavoidable. But techniques are available today that allow patients to remain comfortable during what may be the last months of their lives.

Dr. Lebel noted that — as with other kinds of pain — a comprehensive assessment of the actual cause of pain in cancer is essential to choosing the right therapy. Pain can be the result of pressure from a growing tumor, cancer that has infiltrated the bone, damage to the nervous system, or trauma from a previous surgery.

Any assessment must include an understanding of the preferences and wishes of patients and their families. "Focusing on just the pain without addressing what patients want in terms of quality of life would be doing them a disservice," she noted.

Some therapies that can offer significant pain relief to selected cancer patients tend to be underutilized, Dr. Lebel stressed. These include delivery of anesthetic agents and narcotic drugs directly into the spine through small tubes called catheters, careful cutting of portions of the nerve roots or spinal cord that carry pain signals, and disconnecting the pituitary gland, a procedure which releases natural pain-suppressing systems.

"The neurosurgical techniques may appear very invasive and aggressive, but in good hands they are fairly straightforward procedures. They provide enough pain relief that we sometimes can reduce or eliminate the use of narcotic drugs in cancer patients," she explained.

While the new MGH Pain Center is the hospital's core service for pain treatment, there is also a pain rehabilitation outpatient clinic, run by Raymond J. Maciewicz, MD, of the MGH Neurology Service. He also directs the Spaulding Rehabilitation Hospital's inpatient program for multidisciplinary treatment of chronic pain.

Dr. Carr, who also is an associate professor of anesthesia and medicine at Harvard Medical School, stressed that the new pain center could not exist without many people who laid the groundwork in pain treatment at the MGH over the years. These include the late Henry K. Beecher, longtime Chief of Anesthesia; former Chief of Neurosurgery William H. Sweet, MD; the late Thomas P. Hackett, MD, former Chief of Psychiatry; and Edwin H. Cassem, MD, current Chief of Psychiatry.

One person who worked particularly hard for the establishment of the combined center was Donald P. Todd, MD, longtime chief of the Anesthesia Pain Service, now on the staff of the new center.

"What was really key to pulling everything together," said Dr. Carr, "was the recognition and support of our current Chiefs of Anesthesia and Neurology, Drs. Richard J. Kitz and Anne B. Young."

There are still a lot of misconceptions about pain, added Dr. Carr: "Some still think it's not important in terms of overall recovery or that it's inevitable. But today we know much more. We may not be able to remove all the pain, but in the vast majority of cases we can bring it under control, to a level of intensity that a person can tolerate.

"And we know that improving pain control does help patients recover. It helps them leave the hospital sooner and enables them to stay out of the hospital and resume their lives." ■

# MGH Liver Transplant Program Marks 10 Years

When a team of MGH surgeons performed the hospital's first liver transplantation 10 years ago, the procedure was regarded by some as an extreme, experimental operation of dubious value to patients.

Today, 96 people are alive because they received new livers at the MGH. More than 85 percent of them have returned to the normal, productive lives interrupted by their liver disease (see next page).

The transplant operation is now almost universally accepted as appropriate for patients with end-stage liver disease—who would have no other chance of survival. Several scientific advances have improved the procedure's effectiveness and safety.

A. Benedict Cosimi, MD, now chief of the MGH Transplantation Unit, was a prime mover in establishing the program. He recalled that skepticism about the operation's value led to a vicious cycle in the program's early months.

"Because the first results were not very satisfactory, patients were not referred for transplantation until all other efforts had failed and they were about to die," he said. "It became a rescue attempt on patients who often were comatose, on respirators, bleeding internally; and naturally their survival rate was very low."

Recognition of the need to refer patients for transplantation at the right time in their illness has been an important factor in helping more of them survive.

Also contributing to the improved results are new methods of preserving donor livers. Organs that once needed to be implanted within eight hours of removal now can be preserved for up to 20 hours. The wider time window allows the transplant team to schedule the operation without major disruption to hospital routine.

"Those initial transplants had to be done as emergencies, usually in the middle of the night, with a team going out, getting the liver, coming back and having to put it right into the patient," Dr. Cosimi said. "That resulted in tired surgical teams working under stressful conditions. Often donor livers were lost because a team that had just completed one transplant couldn't do another right away."

The other big scientific advance has been improvements in immunosuppressive drugs, particularly the use of cyclosporine and monoclonal antibodies. The latter are artifical versions of immune system components, designed to suppress the cells responsible for organ rejection.

The most successful of these, OKT3, was first tested in a 1980 research project led by Dr. Cosimi. It proved highly effective in stopping a rejection episode in an MGH kidney transplant recipient. OKT3 is now the treatment of choice for severe rejection of any transplanted organ.

Since the early months of the liver transplant program, the MGH has been part of a statewide consortium — the Boston Center for Liver Transplantation (BCLT) — which also includes Children's Hospital, New England Medical Center, and New England Deaconess Hospital. This joint effort has set a pattern for local cooperative programs subsequently established in heart and lung transplantation.

"The initial idea was to pool resources so that no one hospital would have the whole responsibility for such a resource-intensive project. Instead of competing, the teams could cooperate," explained Dr. Cosimi, who is Claude E. Welch Professor of Surgery at Harvard Medical School.

"For example a team from one hospital would go out to procure an organ, while a team from another hospital prepared the patient and did the actual transplant."

Such cooperation allowed BCLT surgeons to accomplish a then-unprecedented feat — performing four transplants during five days in October 1984 (*MGH News*, December 1984).

BCLT members still share information and cooperate in research. "It's worked out very well both on the patient-care level and in our scientific efforts," said Dr. Cosimi.

In addition to Dr. Cosimi, the current MGH liver transplantation surgical team consists of Hugh Auchincloss Jr., MD; Daniel P. Doody, MD; and Francis L. Delmonico, MD. Surgical fellow John A. Powelson, MD, will join the staff this summer. Gastroenterologist Jules L. Dienstag, MD, is the team's medical director.

Two problems continue to plague all transplant programs — the shortage of donor organs and the remaining limitations of antirejection drugs.

Despite efforts to increase organ donation, the number of donors has remained steady, while the need continues to rise. Most patients wait for months, often in the hospital. From 20 to 25 percent of potential recipients die before an appropriate organ can be found.

Dr. Cosimi notes that, if all appropriate organs were donated, the number of transplants could triple. This would both save lives and actually cut health care costs by reducing the expensive care required by patients with organ failure.

"Ultimately, however, we'll have to find another source; and I think that's going to be another species," he said. Experimental transplants at other institutions, mostly using baboon organs, have not been successful, but Dr. Cosimi and his colleagues are optimistic about future efforts.

Part of that optimism rests on the work of David H. Sachs, MD, who returned to the MGH in 1991 as Director of the Transplantation Biology Research Center and the Paul S. Russell Professor of Surgery at HMS (*MGH News*, March 1991). The miniature swine model he developed, in which genes responsible for organ compatibility can be controlled, is being tested as a possible source for donor organs.

Efforts to improve immunosuppression are targeted toward what may seem a remote goal — inducing a state of permanent immune tolerance to a particular donor's organs. But that long-pursued goal is appearing closer than ever. Researchers hope to introduce selected donor immune system cells into the recipient in such a way that they become part of the recipient's immune system, perhaps via a bone marrow transplant.

"Everybody who's interested in transplantation is working on tolerance," said Paul S. Russell, MD, former Chief of the Transplantation Unit and John Homans Professor of Surgery at HMS. "That's the real solution to the rejection problem."

Dr. Cosimi noted that the ability to induce tolerance would prevent incidents of rejection that occur if patients do not scrupulously follow medication instructions and — more importantly — would eliminate the long-term side effects of current immunosuppressive drugs.

(Another research project that could help patients who now must receive liver transplants is the effort to develop an artificial liver, led at the MGH by Ronald Tompkins, MD, ScD [*MGH News*, September 1992].)

"These two areas — xenotransplantation [use of animals as donors] and tolerance — are going to be the next big breakthroughs in transplantation," said Dr. Cosimi. "And both of them are areas where MGH research can make a significant contribution." ■

# Three of Many Lives Regained Through Liver Transplantation

**Arnold Friedmann,** a professor of art at the University of Massachusetts, developed hepatitis after a vacation in Brazil. His condition deteriorated rapidly — it was later discovered that he also had hemochromatomasis, an inherited condition in which excess iron stored in the body damages the liver.

When he received his transplantation at the MGH in April 1986, Prof. Friedmann was in a coma and critically ill. "I was very lucky they found a liver for me, they tell me I had only 24 hours to live," he recalled.

He was in the MGH for six weeks after the surgery and spent another two weeks in an apartment nearby before returning to his home in Western Massachusetts. Today, at age 68, he is doing "exceedingly well" — able to hike, ski, play tennis, and teach one class a week.

"The people at the MGH were most wonderful. They really took my wife and sons under their wings while I was in the hospital," he said. "Coming for a checkup is like coming home again."

**Leanne Hasse** of Boston was born with biliary atresia, in which the ducts that carry bile from the liver to the intestine do not develop properly. Bile backs up into the liver and destroys liver tissue.

Although Leanne appeared healthy, her condition was diagnosed by blood tests when she was a few weeks old. A surgical attempt to construct new bile ducts failed, and the child was listed for a transplant.

When the transplantation was done not long before her first birthday, Leanne's liver had greatly deteriorated, although outwardly she still appeared well. "Dr. Cosimi told me the liver really couldn't have functioned much longer at all," her mother Nancy Rallis said.

Leanne recovered quickly and today is "a normal little two-year-old," said her mother. "The people at MGH were great, and Dr. Cosimi is just amazing. I thank heaven that he was Leanne's surgeon."

**Sally Johnson,** 45, of Lexington had chronic active hepatitis for 12 years. Her condition remained rather stable until the fall of 1991, when she became seriously ill. She was listed with the MGH transplant program in February 1992 and spent most of the summer in the hospital, being treated for her illness and waiting for a new liver. "I was pretty fortunate in that I could walk around freely, go outside, take a ride with my family. But I still had to be watched closely," she said.

Last September she received her new liver, and her recovery was rapid. She was home in three weeks and, except for some adjustments to her medication, has had no trouble.

"I have back problems from long-term hepatitis treatment with prednisone, which caused me more trouble than the surgery did. Now my back is improving as well. I'm just so grateful to everyone at the MGH." ■

---

# Molecular "Switch" Found for Key Immune Cells

Part of the excitement of scientific research is that no one can be certain where a path of investigation may lead. A search for answers about one disease may lead to information valuable in treating an entirely different condition.

In a recent striking example, a team of MGH basic researchers who had started by investigating a rare inherited disorder of the immune system has found a molecular switch on a key immune defense cell. The ability to block that switch may help prevent a dangerous condition that occurs after serious injury or heart attack and in certain diseases.

For several years, M. Amin Arnaout, MD, director of the MGH Leukocyte Biology and Inflammation Program, has been studying a particular facet of the key immune cells called neutrophils. A type of white blood cells, neutrophils normally defend the body against infections by attacking and eliminating bacteria that have invaded any organ. In a series of pioneering studies, Dr. Arnaout and colleagues had previously linked the infection-fighting ability of neutrophils to a key structure on the cell's surface called CR3.

In those early studies, not conducted at the MGH, the researchers identified an inherited immune disorder called leukocyte adhesion molecule (Leu-CAM) deficiency. Patients with this disease are unable to fight off bacterial infections because their neutrophils are missing CR3.

CR3 is a receptor, a protein that receives chemical signals and stimulates a specific cellular activity. In the case of neutrophils, CR3 receives signals sent out from the site of an infection or injury. The signals switch CR3 into an active form, which enables the neutrophil to move toward and adhere to the damaged area.

Dr. Arnaout, who is also an associate professor of medicine at Harvard Medical School, compares the situation to a house fire (particularly appropriate since the cellular signals are generated by the process known as inflammation). The signal conveyed to the cells via CR3 basically says, "There's a fire here!" It both alerts the neutrophils to the problem and guides them to its location.

In people with Leu-CAM deficiency, the defective CR3 receptor cannot

*(Concluded on Page 8)*

## — Molecular "Switch"

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properly receive the distress signal. The neutrophils are not notified of the inflammation, and any infection can spread throughout the body, often with a fatal outcome.

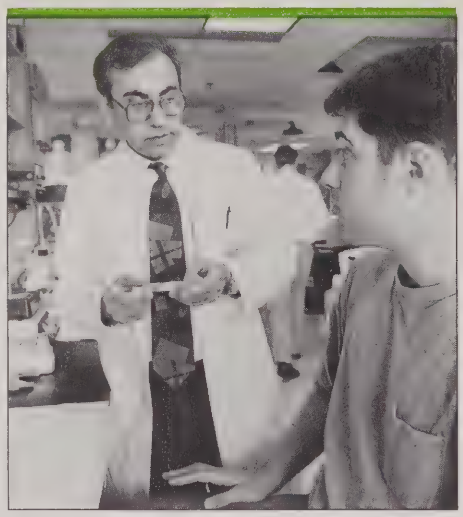
Leu-CAM deficiency patients can be treated with antibiotics and white blood cell transfusions or cured by a bone marrow transplant. But the discovery of the role of the CR3 receptor in inflammation got Dr. Arnaout and other researchers to think about another condition involving neutrophils, one which results from their overactivity instead of inactivity.

If the neutrophils can be compared to firefighters responding to an alarm, they would have to be considered very careless firefighters. Once they arrive at the location of the inflammation, they begin to destroy not only bacteria and damaged tissue but also some relatively healthy tissue as well.

When an injured area is small, the additional lost tissue is insignificant. But a more extensive injury can lead to major tissue loss. Also, when an injury results in a loss or reduction of blood flow to part of the body, oxygen-starved cells send out a similar alarm.

When blood flow resumes, neutrophils rush to the oxygen-depleted areas to destroy damaged cells. But if the blood supply has been cut off too long, the neutrophils are so overactivated that they attack healthy tissue as well, sometimes causing enough damage to shut down a vital organ.

Some situations in which this can occur include heart attacks, in which part of the heart's blood supply is obstructed, and automobile or other accidents, in which significant blood is lost. In addition to direct damage to the areas adjacent to an injury, the whole body can be affected by traumatic shock, an abrupt drop in blood pressure in response to any serious injury.


*Dr. Amin Arnaout (left) discusses mutations to the CR3 receptor with Jim Brayer, lab manager.*

Dr. Arnaout added that the same kind of neutrophil-caused tissue damage occurs in patients with serious burns and is involved in inflammation-related tissue damage seen in arthritis and diabetes. It also limits the amount of time organs can be preserved for transplantation.

"We thought that if we could induce an artificial, temporary form of Leu-CAM deficiency, it might be beneficial in treating these disorders in which the neutrophil is responsible for tissue damage," he said.

Initial efforts to accomplish this have used monoclonal antibodies, specialized immune system cells that would attach to the CR3 receptor and prevent its activity. But the antibodies developed so far are grown using animal tissue and could be attacked by a patient's own immune system.

Now Dr. Arnaout's team has discovered what appears to be a molecular switch on the CR3 receptor. In a report in the March 26 issue of the journal *Cell*, he and colleagues Masahiro Mishichita, MD, PhD, and Viebeke Videm, MD, discovered that a portion of the receptor attaches or binds to certain positively charged molecules often released by damaged tissues, thus enabling neutrophils to attack the injured areas.

When the scientists artificially made cells that lacked this binding site on the CR3 receptor, the receptor could not function. The result implied that the binding site was essential to the stimulation of the receptor and the activity of neutrophils.

"There is no medication that currently blocks the CR3 receptor, and the drug companies have been searching for receptor antagonists [substances that block activity] for some time," Dr. Arnaout said. "This binding site gives them a new, more specific target.

"If we really can shut off this receptor in a selective way, " he added, "it will prevent neutrophils from getting to tissues where they're not needed. The clinical applications could be enormous — from trauma, to heart attack, to diabetes, to organ transplantation — and countless lives could be saved." ■

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MGH News

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# MGH Center Shapes the Surgery of the Future

SOMEDAY — according to the science fiction writers — surgeons will perform operations without cutting into their patients. Marvelous instruments will repair injuries, destroy tumors, and remove damaged organs from outside the body.

Those days are still a long way off — if they ever arrive. But today many operative procedures are already being done through what is called minimally invasive surgery — surgery through several small holes instead of through a large incision.

Minimally invasive surgery is attractive to patients because they generally recover more quickly and have less scarring than in traditional operations. Shorter hospitalizations also lead to an overall reduction in medical costs.

While surgeons in several subspecialties — perhaps most prominently in orthopedics and gynecology — have been using and perfecting minimally invasive techniques for several years, until recently there has been little sharing of concepts and techniques between disciplines around the country.

The MGH Center for Innovative Minimally Invasive Therapy (CIMIT) provides a forum for specialists in several areas to combine their expertise and work together to develop new approaches and applications for minimally invasive surgery. It is believed to be the nation's first such interspecialty program.

"This is a center involving general surgery, radiology, gynecology, thoracic surgery, and the laser laboratories," said

*(Continued on Page 2)*

*Dr. Brian Duncan, senior surgical resident, watches his progress on a television monitor while manipulating an instrument during a laparoscopic procedure. Marian Freehan, RN, holds the tiny camera that transmits a telescopic view of the operation, conducted under the supervision of Dr. David Rattner (not shown).*

INSIDE

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# *New Approach to Aneurysm Treatment Is Saving Lives*

DIANNE HONEYCUTT of Medford was looking forward to several days at New Hampshire's Lake Winnepesaukee as she drove north with her 5-year-old daughter last summer. But her drive was interrupted by the worst headache she had ever had, so painful that she could hardly see.

Somehow she made it to her friends' lakeside cabin and after a brief walk felt better. But several hours later, as she was getting ready for bed, she lost consciousness and tumbled to the floor. Her friends rushed to her side and found she had no pulse.

What happened to Dianne Honeycutt happens to about 28,000 people in this country yearly. Inside her brain an aneurysm — a weak spot that forms a bubble in a blood vessel — had burst, releasing blood into the space between the outer coverings of the brain (a subarachnoid hemorrhage).

The outcome could have been tragic, but Mrs. Honeycutt, 36, was fortunate in several ways. One of those present when she collapsed, Betsy McCarthy, was a nurse who applied the life-support measures that restored Mrs. Honeycutt's pulse.

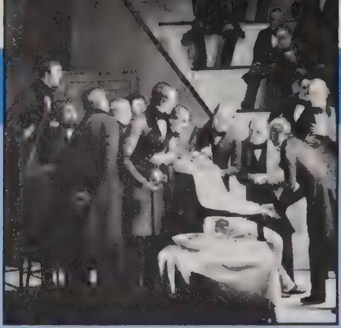
Less than 10 hours after her collapse, Mrs. Honeycutt was at the MGH under the care of neurosurgeon Christopher S. Ogilvy, MD, and other members of the hospital's Brain Aneurysm/AVM Center (*MGH News*, October 1990).

After a thorough evaluation of her condition, she was taken to an operating

*(Continued on Page 4)*

EDITORIAL

# If Only It Were True



Boston teaching hospitals, according to a recent report, are hoarding billions of dollars. The report was written (and paid for) at the request of the head of Boston City Hospital, which has its own new $170 million inpatient building.

The project was created to show that Boston's private teaching hospitals have enough income to help support Boston City, through taxes or some other means.

The local professor hired to write the report used an accounting method that looks at cash on hand and ignores the very present and future debts the cash is held for. Among other oversights are the failure of the report to recognize that hospitals *need* to reserve funds for the replacement of obsolete patient care buildings so inefficient that they are wasteful to operate; that funds donated for specific purposes must legally be spent for those purposes; and that changes expected from health care reform may make teaching hospitals without cash reserves an endangered species.

The MGH itself actually fared relatively well in the report. We were described as having, at the end of 1992, $144 million in available funds, or less than half the amount of a much smaller Boston hospital. Actually, our available cash at that time was only $72 million. *Months* later the figure had shrunk another *$16* million because of payment slowdowns from insurance companies, which pay on behalf of our patients. The remaining $56 million is really not excessive in view of the three-quarters-of-a-billion-dollar (including research) hospital annual operating budget. Certainly not when you consider that the MGH needs $12 million every week merely to meet its payroll and pay for supplies. That means the MGH had only six weeks of cash available for an emergency. That's less than most financial advisers counsel families to have.

The MGH also fared well in the report because it was acknowledged that this hospital was second only to Boston City Hospital among the major teaching hospitals in caring for the uninsured. In an editorial the *Globe* acknowledged that the MGH paid more in lieu of taxes to Boston in 1992 than any other Boston hospital. In fact the MGH has paid about $20 million to governments over a nine-year period. *Contrast that with the fact that all Boston hospitals together own less than 1.5 percent of Boston's tax-free property.* A review of additional facts, some of which have appeared in this space before, is also in order:

Even though we were chartered by the state in 1811 as the *Massachusetts* (not Boston) General Hospital, 6,450 (18 percent) of our inpatients and 183,000 (30 percent) of our outpatient visits are made by people who reside in Boston. At the request of the citizens of three urban communities—at least two of them with major pockets of poverty—we have for years operated major neighborhood health centers: Charlestown since 1968, Chelsea since 1978, and Revere since 1981. Together they had almost 157,000 patient care visits last year, and some 2,300 Chelsea and Revere patients are admitted to the MGH annually.

We provide nearly $30 million a year of care for which we receive no payment from patients—forcing the hospital to depend on the statewide free-care pool, which does not cover the full cost of these services. By far the largest number of nonpaying patients come from Boston.

Let's not destroy our magnet institutions by letting politicians force them to shoulder the burden for a municipal hospital that some of the same politicians themselves have so long neglected. ■

## — *Minisurgery*

*(Continued from Page 1)*

David W. Rattner, MD, Director of CIMIT. "We want to meld our technologies in an effort to look at how surgery's going to be practiced in the next century."

An effort has recently been launched to involve other hospital departments using these procedures in the unified center.

Most minimally invasive surgery done today involves the use of "scopes." These miniature telescopes, inserted through a half-inch incision, allow the surgeon to examine the patient's anatomy and watch the process of an operation on a video monitor. Tiny instruments inserted through nearby punctures are used to cut, remove, or repair tissue.

Arthroscopic surgery, repair of a knee or other joint through such techniques, may be most familiar. However, many of today's techniques were pioneered by gynecologists using laparoscopes, which view the abdomen.

"We've used laparoscopes in gynecology for about 15 to 20 years," said Keith B. Isaacson, MD. "Since the 70s they've been used for tubal ligation [sterilization by sealing the fallopian tubes] and in the diagnosis of endometriosis."

More recently, he added, laparoscopic techniques are being used for removal of ovaries, ovarian cysts, and fibroid tumors of the uterus. Use of a laparoscope in hysterectomy can allow more of these procedures to be done vaginally, rather than via a large, abdominal incision.

"Today, most women who need an ovarian cyst removed can be treated as outpatients and go home the day of their surgery," Dr. Isaacson added. "They can

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PHOTOGRAPHS: All photos by Susan McGreevey. Image on page 3 courtesy of Dr. Robert Novelline.

be back to work in two or three days. Before, the patient was in the hospital for five days and could be out of work as long as six weeks."

The expansion of laparoscopic techniques in gynecologic surgery has been made possible through both greater experience and improved instruments. Dr. Isaacson noted that, as general surgeons became interested in adapting the procedures for their patients, instrument makers had greater incentive to develop new equipment.

Probably the most popular adaptation in general surgery has been laparoscopic cholecystectomy (removal of the gall bladder). While the procedure has spread quickly throughout the country, there has been controversy because some of the earliest operations had unacceptable rates of complications.

Surgeons unfamiliar with the techniques required to manipulate specialized instruments while watching their progress on a monitor risked accidentally nicking a blood vessel or other structure near the gallbladder. The procedure appeared so simple that surgeons at some hospitals were performing the operation after the most cursory training.

MGH surgeons recognized the potential problems at the outset. When the hospital began offering the procedure in 1990 (*MGH News*, September 1990), surgeons were required to take a formal course.

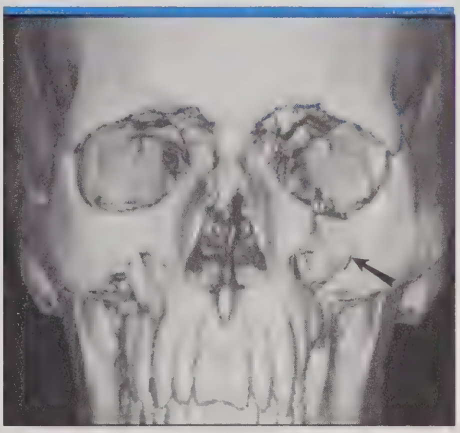
In addition, their first four or five operations had to be done under the direct supervision of a more experienced MGH surgeon. Dr. Rattner — along with Andrew L. Warshaw, MD, associate chief of surgery; and Ronald A. Malt, MD — established an MGH-sponsored course and supervised surgeons and residents as they learned the procedure.

"Even today, patients considering laparoscopic surgery should ask whether their surgeons have taken special courses and how many procedures they've done," said Dr. Rattner. "And the facility must have appropriate nursing and equipment. You need the right team and the right tools to do these operations."

In addition to the gallbladder operation, laparoscopy is being applied to several other general surgical procedures — including removal of some colon tumors and operations to prevent stomach acid from flowing upward into the esophagus. For the time being, these more complex procedures are being performed at the MGH by a team of surgeons including Dr. Rattner, Charles M. Ferguson, MD, and Paul C. Shellito, MD.

In thoracic surgery, John C. Wain, MD, and colleagues are using minimally invasive techniques to remove blebs (blister-like lesions) from the lung and remove some tumors. Neurosurgeon G. Rees Cosgrove, MD, has adapted the procedures to remove tumors and drain cysts within the brain.

Part of the CIMIT research effort is aimed at taking the kind of video images now used to guide minimally invasive surgery a giant step forward. The imaging techniques available through the MGH Department of Radiology — ultrasound, CT scanning, magnetic resonance imaging (MRI), and positron emission tomography (PET) — provide a wealth of information about each patient's anatomy and the chemical activity of various organs.



*Technology used to make this image of a skull may be adapted to produce individual anatomic maps of other organs that will guide surgeons during minimally invasive procedures.*

Modern computer technology allows a consolidation of data gathered from several imaging studies into a single image that can be displayed on a computer screen and manipulated to reflect patient anatomy in three dimensions.

Radiologist Steven L. Dawson, MD, associate director of CIMIT, explained that while this strategy has already been used to plan surgery of the brain and skull, he and his CIMIT colleagues are working on an even greater challenge.

"From an imaging point of view, the brain and the facial bones are simple fixed structures," he said. "When you take an MR image of a brain tumor, its position will not change before the surgery."

However, the positions of organs like the liver, kidney, and pancreas can shift within the body cavity as the patient moves, breathes, or changes position.

Dr. Dawson and his colleagues are working toward finding a way to superimpose data reflecting the position of bodily structures during surgery on the three-dimensional patient anatomy map created before the operation.

He explained, "Surgeons will probably have an ultrasound probe on an instrument — like a headlight in front of a train — to show exactly where they are as they move through an organ. The computer will map the operation's trajectory, projecting ultrasound data onto the previously constructed three-dimensional model."

Dr. Dawson expects that developing this technique will take two to four years. "The most significant hurdle is not the imaging or display, it's finding ways for surgeons to keep track of their tools as motion occurs," he said.

CIMIT research efforts are also aimed at finding better ways to destroy unwanted or cancerous tissue. These may include high-intensity, focused ultrasound — which can be administered from outside the body — and various laser applications.

In addition to Drs. Rattner, Dawson, Isaacson, and Wain, the CIMIT steering committee consists of Marvin C. Guthrie, Esq., Director of Technology Affairs; Ronald S. Newbower, PhD, Vice President of Research and Technology Affairs; Norman Nishioka, MD, Wellman Laboratory of Photomedicine; John A. Parrish, MD, Chief of Dermatology and Director of the Wellman Laboratory; Richard Von Reuden, MD, Administration; and Gerald L. Wolf, MD, PhD, Radiology.

"There are a lot of individual groups around the country doing research into these techniques," Dr. Isaacson said. "But until now there hasn't been a combined center. We expect that what general surgeons are doing may be applicable to gynecology, and we may come up with a technique that thoracic surgeons can use. It's going to be a tremendous advantage."

No one claims that minimally invasive techniques will be adaptable for all forms of surgery. Traditional approaches will continue to be required for many operations — particularly those done on an emergency basis. In fact one of CIMIT's goals is to evaluate realistically whether techniques are appropriate in given situations — from both a medical and a cost point of view.

"What we're talking about sounds very high-tech, but we're not just trying to show off pretty pictures," Dr. Rattner said. "We're trying to do something that will get people in and out of the hospital faster and help them recover more quickly and with less discomfort.

"We could dream up a lot of things to do with this equipment. Figuring out which of them make sense is the biggest challenge of all." ■

# — New Approach Is Saving Lives

*(Continued from Page 1)*

room where Dr. Ogilvy and his team would attempt to close off the aneurysm with a surgical clip.

Mrs. Honeycutt's husband, Steve, arrived at the hospital soon after his wife. He recalled, "Dr. Ogilvy and the others were very honest. They told me how serious Dianne's condition was and that they were going to operate right away. We had to hope for the best."

At another time or in another institution, Mrs. Honeycutt's treatment would have been quite different. In the past, standard practice for patients with a ruptured aneurysm was to wait for as long as several weeks to attempt a surgical repair. It was thought that by giving the brain a chance to recover, there would be fewer problems during surgery.

*Dianne and Steve Honeycutt*

"But if you wait," Dr. Ogilvy said, "a quarter of those patients will have a second hemorrhage within three weeks, which can cause further damage or death. So whenever possible, we do surgery early. And it turns out there aren't as many problems with the operations as everyone expected."

Even more significant was the fact that Mrs. Honeycutt was operated on at all. Patients with a subarachnoid hemorrhage (SAH) can show a range of symptoms — from a slight headache to deep coma and signs of brain damage.

Traditionally those with the most severe symptoms — like Mrs. Honeycutt, who was in a coma — either were put in an intensive care unit until they improved or given comfort measures only. It was thought that operating on them would be fruitless as long as they were in such poor neurological shape.

At the MGH, however, neurosurgeons are talking a more aggressive approach. Following the lead of a group in Arizona, they are closely evaluating patients to find exactly how the SAH caused their neurological condition.

Blood from the aneurysm can form a subdural hematoma, a large clot that exerts pressure on the brain, or a clot within the brain tissue. The clot may or may not be removeable, depending on its location. Excess cerebrospinal fluid (which bathes the brain and spinal cord) also can cause increased pressure. If pressure is not too high, draining the fluid

## Coil is Important Advance in Aneurysm Treatment

THE MGH is one of fewer than 20 hospitals in the world and the first in New England to offer an important advance in treating brain aneurysms. By using the device — known as the Guglielmi coil — physicians can correct aneurysms that are not approachable surgically, either because of their position in the brain or other factors that present a high risk.

The coil is an extremely fine wire made from platinum — one of the softest metals — at the end of a longer stainless steel wire. Several coils, depending on the size of the aneurysm, are inserted inside the bubble-like aneurysm through a catheter (a long, narrow tube) threaded through the patient's blood vessels.

When the coil is in the correct position — verified by a blood vessel X-ray called an angiogram — it is given a positive electric charge. The charge causes the steel wire to dissolve at the point of junction with the platinum coil, and the positively charged coil attracts blood cells to form a clot within the aneurysm.

The coils and resulting blood clot fill up the aneurysm, essentially sealing it off. Eventually the lining of the blood vessel grows over the aneurysm's neck.

In Sup Choi, MD, MGH Director of Interventional Neuroradiology, explained that coil has several advantages over the alternative treatment using tiny balloons.

Balloons have a specific size and shape that may not exactly match the shape of the aneurysm. The soft coil, in contrast, conforms to almost any shape without placing stress on the aneurysm's fragile walls.

Also, the balloons are detached from their inserting catheters by pulling — another source of stress avoided by the electric-charge detachment of the coil.

The coil is named for its inventor Guido Guglielmi, a neuroradiologist at the University of California at Los Angeles (UCLA) and the University of Rome Medical School. It was first used in patients at UCLA in 1990.

Dr. Choi — one of about 25 specialists in the treatment worldwide — noted that the coil does have limitations. It may not be possible to completely fill an aneurysm with a wide neck. In those instances, the aneurysm is filled as much as possible and the patient followed closely for any future increase in the bubble's size.

Since last September, when he arrived at the MGH, Dr. Choi has successfully completed 18 coil procedures.

"The interventional neuroradiologists in our service work very closely with the neurosurgeons and neurologists to select patients who can be treated most effectively," Dr. Choi said. "It is excellent teamwork that is achieving good results." ■

can produce an improvement.

MGH neurologist Daryl Gress, MD, explained, "Traditionally, all patients with major neurological deficits had been lumped together in a uniformly hopeless condition. Now we know we can sort out patients whose prognosis is much better than it originally appears."

Unfortunately, sometimes the examination shows an irreparable problem: the blood clot or aneurysm is located where it cannot be operated on without further damage; loss of bloodflow has damaged an area critical to thinking; pressure inside the brain is too high to safely open the skull.

In Mrs. Honeycutt's case, the surgeons found that simply inserting an instrument to measure pressure and release fluid relieved some of the pressure on her brain. Because her condition improved, and because her aneurysm was in an accessible location, the decision was made to operate.

In an operation that took about six hours, Dr. Ogilvy successfully closed off the aneurysm. Mrs. Honeycutt was taken to the Neuro-ICU. She was still in a coma, her outcome uncertain.

Several days after the operation, Mr. Honeycutt was reading to his wife at her bedside. "All of a sudden one of Dianne's eyes opened, and she looked straight ahead," he recalled. "I called her name, and she looked at me. I asked, 'Can you hear me?' and she nodded. Then I knew she would get better."

Nevertheless, she was just starting on the road to recovery. Over the following days she experienced intense vasospasm, a contraction of blood vessels in the brain, typically occuring four to seven days after a hemorrhage. In the most serious cases, vasospasm can completly shut down an important vessel, causing a stroke.

Dr. Ogilvy, who also is an assistant professor of neurosurgery at Harvard Medical School, explained that the risk of vasospasm is another reason why early surgical correction of an aneurysm is so important. "Standard treatment for vasospasm uses drugs to raise blood pressure and push more blood through the contracted vessel into the rest of the brain. With an unrepaired aneurysm, if you push the pressure up, it'll rehemorrhage. But if you've taken care of the aneurysm, it shouldn't bleed again."

Because of the risk of vasospasm, patients like Mrs. Honeycutt are closely monitored using what is called a transcranial Doppler. An external ultrasound probe measures the speed of blood flowing through the brain's vessels. An increase in the blood's velocity indicates narrowing of the blood vessels.

Rapid identification and treatment brought Mrs. Honeycutt safely through the episode of vasospasm. Soon she began rehabilitation, involving the services of speech-language pathologists, physical and occupational therapists, and other health care professionals.

Mr. Honeycutt also recalls the personal support he received from MGH staff members — nurses, social workers and many others. "One woman really helped me in terms of our daughters, who are 8 and 5," he said. "She discussed questions they were going to ask and what they might worry about. And she was right about everything."

He added that the support and prayers of family members, friends, and countless members of their community were invaluable.

*Dr. Christopher Ogilvy examines an angiogram — a blood-vessel X-ray — showing a brain aneurysm.*

Mrs. Honeycutt soon began recovering rapidly. After four weeks she transferred from the MGH to its major affiliate, the Spaulding Rehabilitation Hospital. She continued with physical, occupational, and speech therapy, with special attention to her biggest problem — her memory.

"I really didn't want to be in the hospital," she said recently, "I wanted to go home. But when I look back, those therapists made a big difference for me. I was weak on one side, and they gave me exercises; they taught me tricks to use for my memory problems."

Less than two months after her aneurysm ruptured, Dianne Honeycutt was at home. In fact, just two days after she left the Spaulding she was able to attend the wedding of Betsy McCarthy, the nurse who helped save her life when she collapsed.

"Today I'm just the way I was before it happened," she said. Her memory problems are gone; she is able to drive and take care of her daughters, one of whom has special needs.

"The children and I are extremely fortunate to have Dianne back," her husband said. "We have nothing but praise and thankfulness for Dr. Ogilvy and everyone at the MGH."

Not everyone whose aneurysm is corrected will recover as completely as Mrs. Honeycutt did. Many factors were in her favor: she was young and generally healthy, and there was no permanent brain damage. But Dr. Ogilvy stresses that her story shows how positive the results can be for a patient who, until recently, might have been given up on.

"A lot is still unknown about why some people recover so much better than others," he said. "Through future research we hope to define which patients will benefit most. If we succeed, we'll be able to tell families, as soon as they come in, whether their loved one has a good chance of getting better." ■

# MGH Clinic Leads in Melanoma Diagnosis, Treatment

FROM ONE perspective, the history of malignant melanoma is a success: over the past 20 years the cure rate for the most deadly form of skin cancer has doubled.

But from another perspective, the news is quite bad, because the worldwide incidence of the disease has grown sixfold during the same time.

Much credit for the success in treating melanoma can be traced to the MGH. Thomas B. Fitzpatrick, MD, now the retired Chief of Dermatology, and his colleagues in the Pigmented Lesion Clinic defined many of the warning signs of early melanoma.

While the term pigmented lesion broadly applies to any colored spot on the body, the MGH clinic is devoted to diagnosis and treatment of melanoma. Founded in 1965, it was the first clinic in the world to bring together dermatologists, surgeons, pathologists, and nurses to provide comprehensive melanoma care. The clinics' cofounders were Dr. Fitzpatrick; Wallace H. Clark Jr., MD, pathlogist; and John Raker, MD, surgeon. Martin C. Mihm Jr., MD, a dermatopathologist, joined the group a year later.

Dr. Fitzpatrick explained that, before he and Dr. Clark began studying melanoma in patients in the early 1960s, physicians could not identify early stages of the disease, which usually develops from a mole, a pigmented spot on the skin.

"One rare, slow-growing type of melanoma was recognized in its early stages. But the commonest tumors were recognized only at later stages, when they developed bleeding and ulceration. In 1965, more than half the patients diagnosed with the commonest melanomas died within five years," he said.

Caught at its early stages, melanoma can be cured by surgical removal. But once the tumor has spread to deeper layers of the skin, there is a great chance that it will metastasize (develop secondary tumors in other parts of the body) and prove fatal.

In the early 1960s, Drs. Fitzpatrick and Clark described two important features of early melanoma lesions: an irregular border and varied color. These easily visible signs permitted recognition of melanoma at a curable stage.

The information was widely shared: an article with color photographs was published in the *New England Journal of Medicine*, and thousands of reprints were distributed by the American Cancer Society. The resulting increase in early diagnosis is believed to be the major reason for the greatly increased rates of survival for the commonest type of melanoma.

Today, between 35 and 40 melanoma patients are seen at the Pigmented Lesion Clinic weekly: those who have been recently diagnosed, those being followed up after treatment, and those being screened because of a suspicious mole or other risk factors.

Arthur J. Sober, MD, Director of the Pigmented Lesion Clinic, noted that several factors can predispose one to melanoma.

### *Warning Signs of Melanoma*

Any change in a wart or mole could be a sign of a skin cancer and should be checked by a doctor. A growth that exhibits one or more of the following signs may be a melanoma, the most serious form of skin cancer.

**Asymmetry** — One side of the lesion does not "match" the other.

**Border** — The borders of the lesion are irregular.

**Color** — The lesion shows several colors — brown, black, blue or red.

**Diameter** — The lesion is 6 millimeters or more in diameter (about the size of a pencil eraser).

**Enlargement** — The lesion has increased in size.

"People at highest risk have a family history of the disease, are light complexioned — blue eyes, blond or red hair — freckle easily, tan poorly, sunburn easily, and had blistering sunburns in childhood or adolescence. Also individuals with large numbers of moles or moles from birth are at greater risk," he said.

A lack of risk factors should not cause one to ignore the possibility of melanoma. "There may be a thousandfold difference between people at the highest risk and those at the very lowest risk, but no one is totally immune from melanoma," said Dr. Sober, who is an associate professor of dermatology at Harvard Medical School.

Early detection (see box for warning signs) is the most powerful weapon against melanoma. Surgical removal while a tumor is still relatively thin (less than 1 millimeter deep) results in what Dr. Sober called "an extraordinarily high cure rate — well over 90 percent survival at ten years."

At later stages, treatment is less successful, although some tumors with limited spread respond to chemotherapy or radiation.

The MGH clinic places a strong emphasis on education — helping patients watch for recurrences or new tumors — screening family members, who are also at risk.

In addition to Drs. Sober, Fitzpatrick, and Mihm, members of the clinic include Raymond L. Barnhill, MD, dermatologist and dermatopathologist; and A. Benedict Cosimi, MD, and Ronald A. Malt, MD, surgeons. Oncology nurse Bonnie Ryan, RN, and dermatology nurse Barbara Graff, RN, play essential roles in patient care.

The alarming increase in melanoma over the past 20 years is believed to result from increased sun exposure — a factor associated with other, less deadly forms of skin cancer as well.

The increasing use and awareness of sunscreens is a positive trend — Dr. Fitzpatrick and MGH colleagues Madhu A. Pathak, PhD, and Edgar Frenk, MD, reported the first effective sunscreen formula in 1969. But many still pursue the look of a suntan, the body's most common sign of solar skin damage.

A growing hazard is the disappearance of the protective ozone layer, which screens out many of the sun's harmful ultraviolet rays. In the 1970s, early reports of ozone loss were dismissed as fanciful. This April, scientists reported that worldwide ozone layers had dropped to their lowest recorded levels.

Dr. Fitzpatrick, who is also the HMS Wigglesworth Professor of Dermatology *Emeritus*, was recently honored by the World Health Organization "for Outstanding Achievements in the Field of Cutaneous Melanoma." He stressed that prevention remains the best way to fight this potential killer.

"We need to alert everyone that melanoma of the skin is virtually an epidemic cancer that is fatal if not discovered early. It is the easiest of all serious cancers to detect by the simplest non-invasive technique — inspection of the total skin surface. Removal of early melanomas results in high rates of survival and cure in very thin lesions. ■

# New Applications for Powerful Cancer Treatment

The new MGH bone marrow transplantation program — the first procedures were performed early in May — is a powerful addition to the hospital's roster of cancer therapies. In addition, research by MGH scientists holds out promise for surmounting some of the current limitations of the technique and for applying it in new areas.

Bone marrow is the soft, spongy tissue found inside the large bones. Most blood cells are produced in the marrow — including red cells and several types of disease-fighting white blood cells.

Some of the most serious conditions affecting bone marrow include aplastic anemia, in which the marrow ceases to function, and the acute leukemias, cancers of the white blood cells formed in the marrow. Bone marrow also can be destroyed by radiation or by high doses of the types of drugs used to treat cancer.

Thomas R. Spitzer, MD, Director of the MGH program, explained that bone marrow transplantation (BMT) has two major applications: "One is a replacement therapy for bone marrow disorders, in which we destroy the existing marrow and replace it with normally functioning marrow. The other is a rescue function, allowing us to treat cancer patients with very high doses of chemotherapy and radiation and restore their marrow with fresh cells," he said.

The former instance, in which the patient's marrow is diseased, requires marrow from a donor (allogeneic). If the marrow itself is not diseased, a sample of the patient's marrow (autologous), may be taken before the treatment and reinfused after high-dose chemotherapy to prevent otherwise irreversible marrow damage.

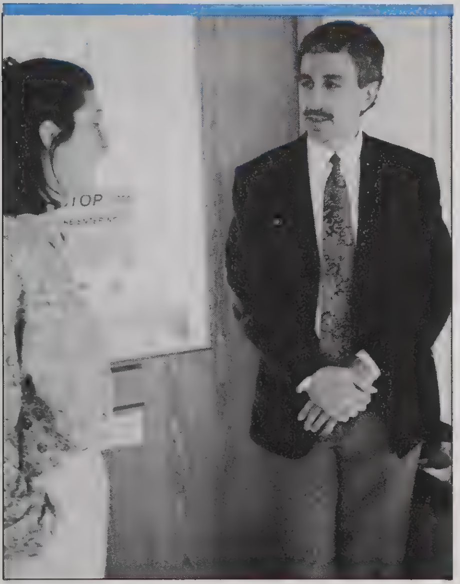
BMT works because of a remarkable property. After marrow is destroyed, new marrow injected into the bloodstream migrates to the marrow cavities in the bones. There it grows and produces blood cells.

The BMT process begins with surgical retrieval of healthy marrow from the patient or a donor. Then the patient receives a combination of high-dose chemotherapy and radiation therapy to either eradicate their cancer or destroy diseased marrow.

Replacement marrow — treated in some autologous cases to remove any contaminating malignant cells — is returned to the patient intravenously, just as in a blood transfusion. It takes two to four weeks for the new marrow to produce blood cells, during which time the patient is highly vulnerable to infection.

Donor BMT presents a unique hazard: graft-versus-host disease (GVHD). Immune cells from donor marrow can attack the patient's organs just as a recipient's immune system can reject a

*(Concluded on Page 8)*



*Dr. Thomas Spitzer consults with Cathy Tosney, RNC, outside a special infection-control room for bone marrow transplant recipients.*

## *Attacking Leukemia From Several Angles*

One of the major applications for bone marrow transplantation (BMT) has been in acute myelogenous leukemia (AML). Scientists also have been researching other ways to treat this blood cell cancer that do not include the risk of graft-versus-host disease (GVHD).

As part of the national Cancer and Leukemia Group B (CALGB), Philip C. Amrein, MD, an MGH hematologist/oncologist, has been testing what is called consolidation therapy. Patients whose cancer goes into remission after initial chemotherapy receive several courses of additional chemotherapy to prevent a possible relapse (*MGH News* September 1987).

The most recent results of CALGB trials show that consolidation therapy produces a cure (defined as five years without recurrence) in about 50 percent of AML patients under 40, a rate comparable to that of BMT. For patients between 40 and 60, who might not be accepted for BMT at some centers, the cure rate was 35 to 40 percent.

On the other hand, Thomas R. Spitzer, MD, head of the MGH Bone Marrow Transplant program, noted that — for patients believed to have a very small chance of cure with chemotherapy alone — BMT offers a special benefit: graft-versus-leukemia effect, in which the donor cells attack any remaining cancer cells. Researchers are working to distinguish which bone marrow stem cells carry this beneficial effect and separate them from cells responsible for GVHD.

Continuing research and fine tuning of treatment programs should further clarify the benefits of the two therapies. Dr. Amrein added that better methods of classifying patients will provide valuable information.

"We're focusing on the exact chromosomal abnormalities found in the leukemic cells. We already know that certain subgroups need a bone marrow transplant while others have a good prognosis with consolidated therapy. As time goes on, our selection methods should continue improving." ■

## — Bone Marrow

*(Concluded from Page 7)*

donor organ.

The risk of GVHD makes it imperative that a bone marrow donor and recipient are matched as closely as possible. Most critical to match are the human leukocyte antigens (HLA), immune system factors that play a major role in transplant rejection.

Because HLA factors are inherited, members of a patient's immediate family have the greatest chance of a close match. Siblings are most likely, but because the antigens are so complex, each sibling has only a 25 percent chance of an exact match.

When no match can be found in a family, a search is made of national HLA registries of volunteer marrow donors. But the chance of an exact match is still limited. To offer BMT to patients without a good match, Dr. Spitzer is launching an investigation of techniques to safely transplant mismatched marrow.

His work will take advantage of research by David H. Sachs, MD, and Megan Sykes, MD, at the MGH Transplantation Biology Research Center. In animal studies, Drs. Sachs and Sykes have found that combining mismatched allogeneic marrow with specially treated autologous marrow can prevent a serious GVHD reaction.

Dr. Sykes discovered that this effect is strengthened by giving the recipient interleukin 2, a substance that stimulates some immune cells. "We think that the IL2 modifies the production of cytokines," she explained. "These substances, made by certain immune cells, may be involved in causing GVHD."

Also being investigated are transplants of peripheral blood stem cells. These precursor (early stage) cells, which develop into blood cells, are formed in the marrow and circulate in the bloodstream. Stem cells can be recovered from the blood and stimulated to reproduce rapidly by recently discovered natural growth factors.

Using stem cells for an autologous transplant has several advantages, said Dr. Spitzer, who is an associate professor of medicine at Harvard Medical School. "There should be less contamination with malignant cells than there is of marrow.

**Transplanting key bone marrow cells may prevent organ rejection.**

"Blood counts recover much more quickly in stem cell transplant," he added. "That has a host of potential benefits, including less infection, shorter hospitalizations, and lower costs."

Kurt J. Isselbacher, MD, Director of the MGH Cancer Center, said, "We were fortunate to recruit Dr. Spitzer from Georgetown, where he had established an outstanding bone marrow program. Among other approaches, his presence will permit us to test the novel approaches being pioneered by Dr. Sachs."

Treatment of leukemia and other blood cancers remains the most common use of BMT (see sidebar). But several new applications are on the horizon.

Certain genetic disorders of bone marrow — sickle cell anemia included — may be cured by transplants of normal marrow. The rescue function of BMT is also being tried in a broader range of cancers, including breast cancer and ovarian cancer.

Barbara L. Smith, MD, PhD, Director of the MGH Comprehensive Breast Health Center, said, "Bone marrow transplantation offers hope for some women whose tumors would not be expected to respond to standard chemotherapy, particularly those whose cancer has spread."

She added, "It has been used for several years in several centers with promising early results. Especially since the toxicity of the procedure has lessened in recent years, it's well worth trying in selected patients."

An exciting possible use for BMT is induction of tolerance to solid-organ transplants. The concept of finding a way to fool the recipient's immune system into accepting a new organ has been around since the earliest days of transplantation.

A. Benedict Cosimi, Chief of the MGH Transplantation Unit, said, "In the future we expect to identify immunosuppressive treatments, given to patients briefly at the time of transplantation, that will create life-long tolerance to the donor organ. Most of the possible approaches involve some kind of cells from the donor, and bone marrow appears to be the best source." ■

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# Rare Genetic Disease Yields to Treatment

THROUGHOUT most of her life, "something" had been wrong with Abby Turner. She never had the inexhaustable energy of a toddler; she bruised easily; she had a series of seemingly minor health problems — particularly abdominal pains — that defied explanation.

Her pediatrician called her "the sickest well child I've ever seen."

As she grew older, her problems worsened. The pains grew stronger, and lab tests showed that levels of both red and white blood cells were dangerously low. Her mother, a nurse, noticed a large mass in Abby's belly. "It felt like her spleen," Linda Turner recalled, "but I thought it

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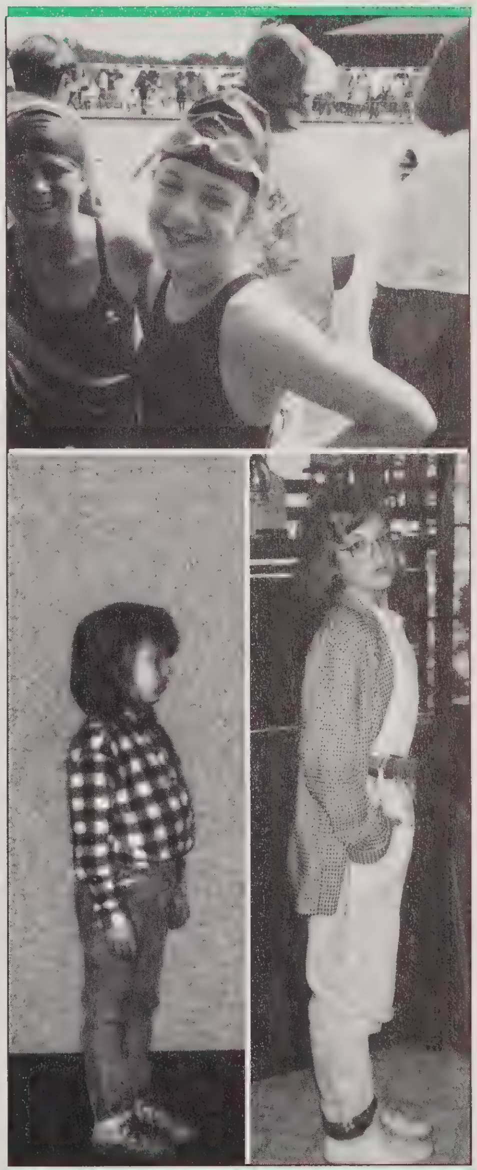

*Today Abby Turner is healthy enough to compete on her local swim team (top). But in 1990 (below left) she had typical symptoms of Gaucher disease — short stature, swollen abdomen, and fatigue. After less than two years of treatment, she had regained a normal appearance.*

# *Behavioral Medicine: Another Tool to Help Patients Cope*

IT TAKES MORE THAN medication to learn to live successfully with a serious illness. Lifestyle changes may be required to improve chances for recovery — and such changes can be very difficult, as anyone who has tried to lose weight or quit smoking can attest.

The impact of an illness profoundly affects patients' relationships and self-esteem. It also is clear that emotional states such as depression, anxiety, and stress have physical effects that may complicate or even confound efforts to regain health.

Members of the Behavioral Medicine Unit in the MGH Department of Psychiatry specialize in helping patients with various medical problems deal with psychological and social factors relating to their illness. At this time, the unit's staff concentrates in three areas: cardiac disease, chronic pain, and children's neurological disorders.

David Ahern, PhD, Director of the Behavioral Medicine Unit, explained that patients with chronic pain — defined as often incapacitating pain that persists more than six months — are at risk for developing significant psychosocial difficulties, primarily depression. He and Tina Wolter, PhD, clinical fellow, participate in the MGH Pain Center (*MGH News*, May 1993) and also evaluate patients referred from the pain rehabilitation group in Neurology and the Oral and Maxillofacial Unit (for facial pain).

"We now know that chronic pain management requires an interdisciplinary approach, not only in terms of assessing the factors involved in pain but also for more effective treatment," Dr. Ahern said. "You can't just treat the underlying physical problem and assume the patient will get better. It doesn't usually work that way."

In close collaboration with specialists from other departments, the Behavioral Medicine staff provides rehabilitative services designed not necessarily to "cure" pain but to improve pain-coping skills and the patient's quality of life.

Dr. Wolter explained that one aspect of behavioral treatment of pain is to help patients manage symptoms without necessarily relying on high levels of medication. "We teach them alternative

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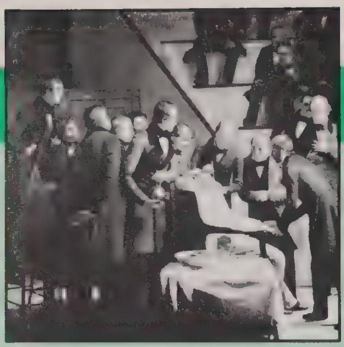

## National Health Care Reform

THE LONG-AWAITED national health care bill is scheduled to emerge later this month from the White House. As a candidate last year, President Clinton advocated limiting the country to one or two health insurers. Such a drastic change would reduce health care costs significantly by eliminating mountains of paperwork for providers of health care. The politics of eliminating so many insurers, however, makes that course about as likely to happen now as the nation is likely to abandon democracy for monarchy.

High technology is another major contributor to costly medical care. One way to restrict the use of high tech medicine would be to limit its insurance coverage to tertiary rather than primary care. Developing a list of which technologies could be used to diagnose what symptoms might be one way to moderate these costs. But deciding whether the primary caregiver or a specialist should order a test or treatment might be just one source of difficulties.

Some form of managed care (such as HMOs) is likely to become a basic tenet of the Administration's plan. The patient entering many managed care programs has a restricted ability — or none — to choose a physician. Whether a large part of the American public is ready to accept that loss of freedom remains undetermined.

A fundamental principle of managed care is that primary caregivers (generalists — like internists, pediatricians, and family practitioners) will be the gatekeepers who decide when a patient needs to see a specialist or enter the hospital. But there are not enough primary caregivers for a nationally mandated managed care system. To train more generalists and fewer specialists, the government will probably pressure teaching hospitals by providing them less money to train the country's doctors unless those hospitals predominantly teach generalists.

At some point, however, human nature is likely to sabotage the country's long-term needs. The United States tends to swing wildly from one end of a spectrum to another. Whether it is a new system of education, a new craze in music, or a new medical procedure, we seem to greet novel ideas with unrestrained enthusiasm, only to find that we have overreacted. Ultimately we swing back to the opposite pole of cynicism without even a pause at the middle. What is most likely is that we will train so many generalists that in 10 to 15 years we will suffer a major shortage of specialists available to treat problems beyond the training and expertise of the generalists. Wouldn't it be better now to set goals for a reasonable balance between generalists and specialists?

Similarly, support for teaching hospitals is likely to erode because they have "an overabundance of costly specialists and high technology." But no matter how much emphasis we place on preventive care and primary care, an aging population is going to need more tertiary care to provide older individuals with extra years of high-quality life. Reconstituting teaching hospitals in 10 to 15 years would be many times more expensive than choosing and preserving national centers of excellence now.

There is much to be said for universal health care. But let's get it right. ■

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## —Behavioral medicine

*(Continued from Page 1)*

coping strategies and look at how they think about the pain and its effects on them," she said.

"For example, instead of responding to an episode of pain by thinking, 'Oh no, my pain is getting worse,' they can learn to take a different approach. 'What can I do to control my pain?' "

One helpful tool is relaxation training, techniques that release physical tension in the muscles and quiet thinking to reduce emotional stress. These can include deep breathing, consciously relaxing muscles throughout the body, and concentrating on soothing words or images.

"As patients get more comfortable with the techniques, they find that just a few deep breaths can produce the kind of relaxation that used to take 15 to 20 minutes," Dr. Wolter said.

"It also helps them become more aware of what's happening with their bodies. Patients might tell me they were driving and noticed their shoulders were tense. They were able to release the tension before it triggered an outbreak of pain."

Another useful technique is biofeedback, which uses a visual representation of usually unconscious physical responses as a guide to help patients relax specific muscles. An added approach is behavior modification to help patients set reasonable goals without overly restricting their activities.

"On the one hand, almost all patients routinely push their pain tolerance, which produces a vicious cycle of pain, re-

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PHOTOGRAPHS: Page 1. courtesy of Linda Turner; pages 3,4,6,8 Susan McGreevey; page 7 image courtesy of Dr. Maya Jerath.

stricted activity, and more pain," Dr. Ahern explained. "On the other, families members, in an effort to help patients, may become overprotective, increasing patients' sense of helplessness."

Working with patients and family members to analyze behavior patterns and family interactions can encourage an appropriate increase in independence and greater pain control.

Dr. David Ahern

"When patients ask me, 'What will happen to the pain?'" Dr. Ahern added, "I use the metaphor of a stove with four burners. When pain is bad, it's like a pot of water boiling on the front burner.

"After appropriate treatment, that pot is moved to the back burner and the stove turned down to simmer. The pain will still be there, but the patient can manage it."

The connection between cardiac disease and behavioral factors such as diet, exercise, and stress is well recognized. Milagros Rosal, PhD, of Behavioral Medicine works with the Cardiac Rehabilitation Unit staff to address these issues. Along with psychiatrist Andrew Littman, MD, she evaluates patients to try and head off possible problems they may have in following their treatment plans.

"A typical patient may be a man who is very successful, runs his own business, and then has a heart attack at an early age," Dr. Rosal explains. "He now is facing a lot of doubts about his future as a businessman and about his role in the family.

"From my perspective, this is someone who will probably have a great deal of trouble following his prescription — the exercise, diet, and medication — unless we help him address his fear that he won't be the person he used to be," she added.

As with the pain patients, a primary goal is for patients to regain a sense of control over their health. Dr. Rosal helps them set realistic goals, monitor their behavior, and practice how they will deal with difficult situations.

Communication skills are particularly important — both to help patients share concerns with their family members and colleagues at work and to encourage them to discuss questions and issues openly with their physicians and other health care providers.

An unexpected facet of a family's reaction to cardiac disease is being addressed in a national study being conducted at the MGH and five other hospitals. It is often recommended that a spouse or family member of a patient recovering from a heart attack learn cardiopulmonary resuscitation (CPR) to help the loved one survive a possible future attack.

It has been discovered, however, that very few family members actually learn the technique. Even fewer try to use CPR if a subsequent heart attack does occur — possibly because of fear of making a mistake or difficulty handling the responsibility.

"If the family breadwinner has a heart attack and the spouse learns CPR, that can represent a major shift in the dynamics within the family," Dr. Ahern said. "The spouse may be overwhelmed by the prospect of being in control of a potentially life-or-death situation."

*Dr. Tina Wolter (left) guides Margaret Dwyer through relaxation exercises while tracking the temperature of her hands — a measure of relaxation — on a biofeedback monitor.*

The study, conducted in cooperation with the Cardiac Rehabilitation Unit, offers family members standard CPR training in combination with special educational videotapes that cover different aspects of heart disease and its effects on family members. The goal is to identify ways to increase the use of CPR by addressing often-hidden family concerns.

The emotional impact of illness can be just as strong for children as adults. Bruce Masek, PhD, has been providing pediatric behavioral medicine services at the MGH since 1986 and joined the Behavioral Medicine Unit when it was established last year. He also is Chief of Behavioral Medicine at Children's Hospital.

Many of his young patients have neurologic problems leading to migraine headaches or other chronic pain conditions. Others may have had intestinal surgery related to a birth defect and need to learn new ways of using muscles to control their bowels.

"The difference between adults and children in behavioral medicine is not as great as people might think," Dr. Masek said. "Biofeedback techniques are very useful in helping children control pelvic floor muscles. Children easily learn relaxation techniques, possibly even more quickly than most adults do."

He described how a child with migraines might wake up in the morning feeling that "it's going to be a headache day. You can use your relaxation skills — use them 30 seconds here, 40 seconds there during the day — and probably prevent or at least lessen the severity of the headache."

Dr. Masek added that the involvement of parents is essential. "You need to make parents part of the solution to the child's problem. You can teach them how to support the child's efforts to adapt and learn control of their illness, and they become real partners in the child's care."

Dr. Ahern hopes that the unit's efforts can soon expand to serve patients with other illnesses, like diabetes, in which behavior is critical to maintaining good health. He stresses that the integration of behavioral medicine with more traditional medical techniques can no longer be regarded as unconventional or experimental.

"At some levels, society still tends to regard the mind and body separately. But that is absolutely incorrect," Dr. Ahern said. "Psychosocial and behavioral issues are critical to the promotion of health. Most of the serious diseases we face today are not so much cured as controlled or, even better, prevented."

***"Techniques that help patients control their behavior can be a powerful tool in containing health care costs and improving the overall health of people in this society."*** 🟩

# — Rare disease yields to treatment

*(Continued from Page 1)*

couldn't be. It was much too large!"

At the age of 8 Abby was hospitalized; her doctors and family feared she had leukemia. But extensive tests were inconclusive until one member of the treatment team at Bay State Medical Center in Springfield had another idea.

He thought Abby might have a storage disease — a malfunction of the body's systems for disposing of unwanted material. The hunch was right. Abby had a genetic condition called Gaucher disease. People with Gaucher are missing an enzyme required to break down a molecule found in worn-out red blood cells.

The disease causes enlargement of the spleen and liver, deficiencies of red and white blood cells, and pain and deterioration of bones (see sidebar, next page). Although many people live for years with few symptoms, for others it can be debilitating, even life-threatening.

The gene defect that causes Gaucher occurs more frequently in Jews of Eastern European (Ashkenazi) ancestry, but the disease can occur in almost any ethnic group. Like Abby Turner, many Gaucher patients are not Jewish.

While the diagnosis solved the mystery of Abby's illness; it didn't offer her family much hope. At that time — in 1988 — there was no treatment that addressed the enzyme deficiency behind the disease.

MGH Chief of Orthopaedics Henry J. Mankin, MD, is a national leader in care of Gaucher patients. He noted that, for many years, physicians could only treat the symptoms of the disease.

"When patients came to us with bone fractures or collapsed joints, we could offer mechanical devices like total joint replacements. We could treat infections, give them blood products or pain medications, but there was nothing we could do to really make them better."

Removal of the spleen was often a last resort when the organ's size and its accellerated destruction of blood cells threatened to become overwhelming. But that procedure poses additional risks. Patients become more susceptible to infections, and bone problems tend to increase.

Abby received most of her care at Bay State, but she also was referred to the MGH Neurogenetics Clinic, then directed by Edwin Kolodny, MD.

"Abby's original prognosis had been pretty bad," said Mrs. Turner. "The doctor who made the diagnosis said she'd still be here in five years, but he wasn't very encouraging. We thought she was dying. It wasn't until we came to the MGH and talked with Dr. Kolodney and Dr. Short [M. Priscilla Short, MD] that we got the first indication that Abby might survive."

Dr. Short — who is now co-director of the Neurogenetics Clinic, along with Katherine B. Sims, MD — has overseen Abby's care ever since. Both physicians also are assistant professors of neurology at Harvard Medical School and care for several Gaucher patients.

For the next two years, Abby was treated for increasingly severe episodes of abdominal pain. She began to have bone problems. It was difficult for her to eat enough to maintain her weight. Her swollen spleen pressed on her stomach so that she could eat no more than a few bites of food at a time, even though she constantly felt hungry.

Her family was sustained by the hope that an effective treatment for the disease was on the horizon. That treatment was a specially-altered form of the enzyme missing in Gaucher patients. Roscoe Brady, MD, of the National Institutes of Health had discovered a method of targeting the enzyme so that it would travel directly to the "Gaucher cells" that accumulate in the spleen, liver, and bone marrow.

Dr. Mankin and Samuel Doppelt, MD, of the MGH Orthopaedics Department, conducted the first patient trials showing that enzyme replacement therapy could reverse Gaucher symptoms — spleen and liver size decreased, levels of blood components rose, bone structure appeared to improve.

The US Food and Drug Administration approved the treatment for Gaucher in April 1991. A month later Abby Turner became one of the first patients in New England to receive the drug alglucerase (Ceredase) on a non-experimental basis.

Within a matter of weeks, she began to feel better; within months, her spleen was noticeably smaller. After two years of treatment Abby, now age 13, has grown almost a foot taller. Her abdomen is a normal size, and she has the energy to — in her own words — "do pretty much anything I want."

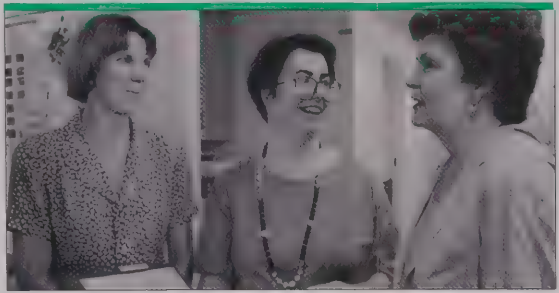
While enzyme replacement offers the first effective treatment for Gaucher, it presents several dilemmas. Produced by the Genzyme company, the drug is extremely expensive. A year's treatment can cost from $20,000 to $200,000.

Genzyme assists patients in obtaining insurance coverage for treatment and, as a last resort, even provides the drug free. Researchers are addressing costs by trying to define exactly when treatment should begin and finding the smallest dose required to produce relief from symptoms.

Dr. Sims noted, "If this therapy cost a few cents, anyone who had the disease could get the enzyme replacement as long as there were no other problems. But because of the cost, we're trying to make sure we're using it when it's really needed."

At this time most patients with symptoms severe enough to lead to a Gaucher diagnosis are eligible for treatment.

Also needing answers are questions related to dosage. How should adjustments be made as patients' health improves? Will treatment need to continue throughout life?



*Drs. Katherine Sims (left) and Priscilla Short (center) discuss the progress of a Gaucher patient with nurse specialist Catherine Bove, RN.*

And treatment is not a simple proposition. Alglucerase must be given intravenously — usually in a hospital — every two or three weeks. Therapy means a significant time commitment for people who may have found ways of accommodating their disease for many years.

For some — perhaps most — that commitment probably will be worth it. And a group of MGH researchers has just launched an effort to investigate the real impact of enzyme replacement on the lives of Gaucher patients.

The three-year quality-of-life study will follow a group of patients — adults and children — to measure the psychological and social aspects of living with the illness. All patients with Gaucher who enroll in the study will be tracked to measure the changes the disease itself — as well as therapy, if initiated — makes on their lives.

Dennis Norman, PhD, MGH Chief of Psychology and principal investigator for the study, explained that participants will periodically complete standard written psychological questionnaires and participate in a face-to-face interview with a mental health professional.

"Little has been done to study the impact of serious illness on quality of life," said Dr. Norman who also is an associate professor of psychology at HMS. "This is the first time we've done a study when a successful treatment was available. It offers a unique opportunity to document not just the medical benefits of treatment but the impact on a patient's entire life."

Other Gaucher research at the MGH includes a study led by Dr. Mankin. He and colleagues already had shown that treatment could reverse bone destruction in patients who still had their spleens.

The newest study will explore whether the same effect can be produced for those who have had the organ removed, who typically have more serious bone problems.

"We expect enzyme replacement will help these patients even more, because they need it more," said Dr. Mankin, who also is the Edith M. Ashley Professor of Orthopaedic Surgery at HMS.

Longer term goals for improved Gaucher therapy include finding less expensive ways to produce the enzyme replacement. The ultimate treatment would be gene therapy, which theoretically could induce the patient's body to produce the missing enzyme. While that would "cure". the disease, many problems remain to be solved before it becomes practical.

But for Abby Turner and her family, enzyme replacement has made all the difference. The past two years have not been without problems, some related to adjustments in medication to compensate for her rapid growth. But her mother says that today Abby is "as energetic and active as any 13-year-old could be."

And throughout they have relied on the knowledge and support of MGH staff. "Without Dr. Short, I don't know where we would have been," Mrs. Turner said. "I often picked up the phone to call her when we had problems, and she always helped us find the answers." ■

## Gaucher Effects Seen Thoughout the Body

Gaucher disease is a genetic ailment in which the body does not produce enough of an enzyme called glucocerebrosidase (GCR). Gaucher occurs when someone inherits two defective GCR genes, one from each parent. People with only one defective gene are Gaucher carriers, but are not affected by the illness.

GCR is active in immune cells called macrophages. Among other duties, macrophages ingest worn-out cells and break them down into smaller molecules for excretion from the body.

GCR's function is to break down a fatty substance called glucocerebroside, found in the outer wall of red blood cells. Without GCR, glucocerebroside accumulates inside macrophages. Swollen with the material, cells no longer function normally but also cannot be destroyed by the body's normal cell-breakdown mechanisms.

These "Gaucher cells" accumulate in three primary locations — the spleen, the liver, and the bone marrow. The spleen typically becomes greatly enlarged, swelling a patient's abdomen to what may be huge proportions.

The spleen's job is to break down old blood cells, and in Gaucher the oversized organ is also overactive. Red blood cells are destroyed faster than they can be replaced, so patients become anemic. White blood cells (part of the immune system) and platelets (active in blood clotting) also become deficient, increasing the risk of infections and excess bleeding.

The liver also may become enlarged with Gaucher cells, and its function may be affected, although not as dramatically as with the spleen. But cells accumulating in the bone marrow lead to very serious problems.

Gaucher cells interfere with the normal function of bone marrow, reducing the production of blood cells and increasing the deficiences caused by an overactive spleen. Bones may become thin, porous, and deformed. They are prone to fractures, infection, and death of bony tissue.

A sudden cutoff of blood supply to an area of bone causes "Gaucher crisis," characterized by excruciating pain, fever, and dehydration that may require hospitalization. The pain of a crisis can last for several weeks.

One of the many mysteries about Gaucher is how differently it can affect patients. Some people can lead normal lives. Others experience serious complications that sap their energy, restrict their mobility, and may threaten their lives.

There actually are three forms of Gaucher. The most common, Type 1, affects the organs described above and shows a wide variety of symptoms and severity. Type 2, which affects infants, and Type 3, affecting young children, additionally involve the nervous system. Both of the latter forms are extremely rare.

Type 1 Gaucher genes are found in fewer than 1 in 40,000 people in the general population, but in 1 in 400-600 among Ashkenazi (Eastern European) Jews. While largely unknown in many areas of the country, among the general population Gaucher is as common as hemophilia. ■

## *Symptoms May Be Unrecognized*

The gene defect underlying Gaucher disease is present throughout life, but symptoms can appear at any time from infancy to old age. Symptoms may be mild or very serious, and physicians unfamiliar with the disease may attribute them to another illness. Following are some symptoms resulting from infiltration of "Gaucher cells" into the organs.

***Spleen*** — Distended abdomen; anemia (low red blood cell count); fatigue; uncontrolled bleeding (low platelet count); infections (low white blood cell count).

***Liver*** — Distended abdomen; cirrhosis (rare).

***Bones*** — Low levels of blood cells; bone pain; thin, fragile, or deformed bones; fractures; infection or death of bony tissue. ■

# Yvonne Munn Caps Her Career at the MGH

Generosity, wisdom, inclusiveness, breadth of vision, compassion for patients: these are several of the terms used by colleagues to characterize Yvonne L. Munn, RN, MSN, who retired this summer as MGH Associate General Director and Director of Nursing. She had led the Department of Nursing since 1984.

During her nine-year tenure, Mrs. Munn worked to improve recognition of staff nurses, championed the role of the nurse manager, and built strong collaborations with other departments in the hospital.

Both the MGH Center for Research-Based Practice and the Harvard Nursing Research Institute — which she played an important role in establishing — embody her conviction that nursing is and should be a practice based on acquired knowledge and scientific principles, combined with compassionate caring.

Mrs. Munn explained that many people mistakenly look on nursing activities as intuitive — that decisions are reached based on a nurse's "knowing what to do," rather than on an analysis of facts.

"A common example is in the critical care unit, where a seasoned practitioner may be able to just look at patients and know they are about to go into a crisis," she said. While the process of reaching that judgment may be unconscious, it is based on knowledge that has been accumulated over the years, not on just intuition.

That observation has several implications. One is that the information nurses use to make decisions about patient care can be analyzed and studied like any other scientific data. Another is validation of the professional status of nursing — that it is based on a body of knowledge, not just a set of technical skills.

That professional quality is seen at all levels of nursing, from the staff nurse at the bedside through the nurse manager who oversees and coordinates the innumerable aspects of running a patient unit.

"I have tried to enhance recognition of the importance of staff nurses to patients and their families," Mrs. Munn said, "and, probably more subtly, to help nurses to recognize their own professionalism. And one of the rewards I've experienced is hearing the staff nurses reflect that increased sense of self-worth back to me."

She noted that the nurse managers — formerly head nurses — have significantly expanded their roles at the MGH and at hospitals around the country. "At the MGH, nurse managers coordinate all the caring functions needed by the patients in their units, administer budgets of several hundred thousand dollars, and manage and support staffs of 30 to 50 people. Any way you look at it, that's a small business.

"When you add to that their clinical expertise, the impact they have on quality of care, I think they have a tougher job than I do."

Throughout her advocacy of nurses and nursing, Mrs. Munn maintained a focus on the importance of collaborative relationships with nonnursing professionals. She stressed that only by drawing on the strengths of all patient care disciplines — nursing, medicine, dietetics, social work, physical therapy, and many others — can hospitals meet all patient needs.

Strong collaboration with chief nursing officers at the other major Harvard hospitals — Beth Israel, Brigham and Women's, Children's and New England Deaconess — led to last fall's establishment of the Harvard Nursing Research Institute, based at the Harvard School of Public Health. The institute, which will offer research fellowships to nursing professionals with doctoral degrees, is the first nursing program at Harvard University.

While MGH nursing research now is based in the new Center for Research-Based Practice, Mrs. Munn noted that the effort has evolved over several years. "At an institution like the MGH, where we have a rich intellectual climate and outstanding medical researchers, it seems natural to encourage and develop those skills in our nurses, apply for research grants, and study nursing interventions in a scientific way."

The many resources of the MGH, first of which are its people, are key to the hospital's ability to respond to the challenges facing all health care institutions, said Mrs. Munn.

"This organization has so many ways in which it could respond to change. There's a wonderful spirit, a readiness among a lot of people — not just nurses — to work on finding better ways to care for patients in the hospital, in the clinics, and in the health centers," she said.

"I've said to so many people that my years at the MGH have been a wonderful way to cap a career."

Mrs. Munn is a graduate of the University of Alberta in Canada and received an MS in Nursing from the University of California, San Francisco. She held nursing education and administrative positions at Edmonton (Alberta) General Hospital School of Nursing, Medicine Hat (Alberta) General Hospital, and Sharp Memorial Community Hospital in San Diego.

*Yvonne Munn, RN, MSN*

In 1969 she joined Presbyterian-St. Luke's Hospital (later Rush Presbyterian-St. Luke's Medical Center) in Chicago, where she eventually became assistant vice president for nursing and associate dean of the College of Nursing. She moved to Methodist Hospitals of Dallas in 1977 and was vice president of nursing services, patient services, and patient systems and evaluation. In 1984 she came to the MGH.

Among her many honors, she recently received the Theresa La Plante Award of the Sigma Theta Tau International nursing honor society and was named professor emerita at the MGH Institute for Health Professions. The MGH Department of Nursing also has established the annual Yvonne L. Munn lectureship. ■

# Lasers May Be Key to Improved Burn Surgery

THE PRECISION and power of the laser — a concentrated beam of light — has been used by physicians to conduct delicate surgery, destroy unwanted tissues, and remove disfiguring birthmarks and tattoos.

Now researchers at the MGH Wellman Laboratories of Photomedicine are developing techniques using lasers to improve treatment of one of the most devastating injuries: serious burns.

The project draws on the MGH's years of investigations in photomedicine — the use of light, including lasers, in the treatment of disease — as well as the hospital's international prominence in burn care.

Serious burns require surgical removal of almost all burned tissue to prepare for skin grafts. But surgeons are often faced with a dilemma.

Superficial burns, which do not require grafting, and very deep burns that penetrate beneath the skin are easily diagnosed by visual inspection right after the injury. However, many burns are not so easily evaluated. Even the most experienced specialists find it difficult to predict whether these indeterminate-depth burns require surgery.

"What is typically done," said Robert L. Sheridan, MD, a surgeon at the MGH and affiliated Shriners Burns Institute, "is to treat the burns with a topical antimicrobial agent and watch them closely for several days. Usually between three and seven days you are able to tell where you need to operate and where you don't.

"The delay that's inherent in managing indeterminate-depth burns means that patients have to endure days of discomfort — including several painful dressing changes — and spend more time in the hospital."

When surgery is carried out, the line of demarcation between the burned and healthy skin is often unclear to the surgeon guided by vision alone. Not removing as much of the burned tissue as possible would leave the patient open to infection and keep skin grafts from adhering.

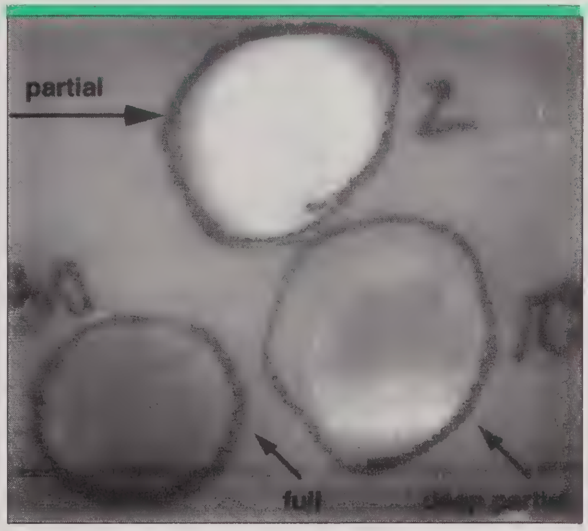
Preservation of healthy tissue to help patients recover maxiumum function is always a goal in burn surgery. In addition, removal of too much tissue can cause excessive bleeding (a problem somewhat alleviated by improvements in surgical techniques), which poses a real risk for patients already faced with a serious injury.

The MGH research project is working on two steps toward improving burn surgery — one, an improved method for diagnosing burn depth, and the other, a way to more accurately remove burned tissue with little or no blood loss.

Norman S. Nishioka, MD, of the Wellman Labs and the MGH Dermatology Department is leading the effort. He explained that the diagnostic system is based on the interaction of light with special dyes that can be injected into the bloodstream.

"One dramatic difference between unburned and burned tissue is that one has bloodflow and the other does not; blood vessels in the burned skin have been sealed off.

"When one of these harmless dyes is injected, it is carried wherever the blood goes. By probing the burned area with certain types of light, we can detect the presence of the dye, which indicates how deep the burn is."



*Images from a prototype burn diagnostic system show burn depth by intensity of a fluoresence signal. Superficial burns (partial) reflect a bright signal while deep burns (full) appear darker. The dark portions of the indeterminate-depth (deep partial) burn indicate areas requiring surgery.*

When light interacts with the injected dye, it emits a signal called fluoresence. A beam of infrared light produces an intense fluoresence signal when reflected from dye in blood vessels near the surface — indicating a shallow burn. If the light must travel further to encounter blood vessels, the signal is much fainter, indicating a deeper burn (see illustration).

A prototype diagnostic system, tested in animals, will soon be tried in volunteer burn patients.

The project's second stage investigates the use of lasers to ablate or destroy the actual burned tissue. The laser offers not only microscopic precision in tissue removal — potentially leaving less dead skin — but it also seals off the topmost level of living tissue, practically eliminating bleeding and perhaps improving the results of skins grafts.

The overall goal is to combine the two aspects into a single system where the fluoresence diagnostic information would guide the surgeon during an operation and, under computer control, could automatically stop the laser when healthy tissue is reached.

Both Dr. Nishioka and Dr. Sheridan, who will help conduct patient tests of both systems, noted that the particular carbon dioxide ($CO_2$) laser used in this technique will require very delicate control.

"The $CO_2$ laser technology is what we call scaleable — we can make it larger and more powerful — which should allow burns to be removed much more quickly," Dr. Nishioka said. "But with such a powerful laser — stronger than anything now used in medicine — it's important that exposure time be limited.

"There are two ways to accomplish this. One is a pulsed laser, where the beam is constantly turned on and off. The other is a scanned system, where the beam is constantly moving."

Dr. Sheridan added, "There are a lot of logistic issues involved in treating an actual patient. The surfaces are not flat. The burns are irregular in depth, and there are superficial structures that cannot be injured."

To address these control issues, the Wellman scientists have recently entered an agreement with Sandia National Laboratories, a US Department of Energy facility with expertise in sophisticated

*(Concluded on Page 8)*

## — Lasers

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engineering.

"A project like this becomes so complicated it exceeds our engineering capacity," said Dr. Nishioka who is also assistant professor of dermatology at Harvard Medical School.

"Sandia is very good at developing fail-safe systems that would prevent an extremely powerful laser system from harming a patient, or even someone else in the operating room, if something goes wrong."

Sandia's engineers also will take a major role in developing the combined diagnosis/treatment system and its associated computer and robotic elements. As currently projected, the effort is expected to take four years.

John Parrish, MD, MGH Chief of Dermatology and Director of the Wellman Labs, said that this joint effort is a good example of cooperation between academic medical institutions and the government.

"The Department of Defense is providing funds, Sandia Labs is providing engineering and technology, and the MGH brings its multidisciplinary experience in combining basic, applied, and clinical research with innovative patient care. When the time comes, an industrial partner will be selected to make new diagnostic and treatment systems available on a widespread basis."

Dr. Nishioka added that this project's success could lead to broader application of the technique. "The concept used here — laser tissue removal prior to grafting — could be generally applicable to conditions such as skin tumors, deep ulcers, and even cold injury such as frostbite."

Each of the complex questions that must be answered presents a possible barrier to development of a safe, practical system for treating patients. But the effort should almost certainly provide important new information about the biological interaction between tissues and lasers — information that could lead in unexpected directions.

Ronald G. Tompkins, MD, ScD, MGH Chief of Trauma and Burn Services, noted, "Even though laser surgery may not prove practical in burn treatment, there will be many other potential applications of this therapy."

"The $CO_2$ lasers that have been tried in the past to remove eschar [burned tissue] have had mixed, unsatisfying results," said Dr. Sheridan, who also is assistant professor of surgery at HMS. "But this is a completely different way of using this energy, and to our knowledge, no one else is doing this." ■

*Maya Jerath, PhD, Wellman Labs research fellow, examines images from the prototype burn diagnostic system. Above her head are the unit's infrared lights, sensors, and lenses.*

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# MGH News

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*MGH nurse practitioner Robin Sherman visits Frances Ford in her Chelsea home.*

## Health Centers Embody 'the MGH at Its Best'

THE PUBLIC FACE of the MGH is one of the world's leading hospitals: a huge complex of buildings on the banks of the Charles River where high-technology medical care is delivered to thousands of patients and where scientists work to uncover the latest medical mysteries.

But for residents of the communities of Charlestown, Chelsea, and Revere, the face of the MGH can be the physician who delivers primary care to an entire family — from infants to grandparents.

The MGH is the nurse who provides care and answers questions in a high school clinic; the nurse practitioner who delivers prenatal care to an expectant mother; the medical resident who visits elderly patients in their homes; the administrators who work with community leaders to address problems of drug abuse, violence, and infectious disease.

Each of the MGH-affiliated community health centers is dedicated to meeting specific local needs, along with giving its patients access to the full range of services offered by the hospital. At a time when issues of access to health care and providing cost-effective services are paramount, the MGH centers are an example of how a large, teaching hospital can serve people in what might otherwise be medically underserved communities.

***The Bunker Hill Health Center (BHHC) in Charlestown was founded 25 years ago***, in September 1968, with the late John P. Connelly, MD, as Executive Director. The first MGH neighborhood center was only the second community health center in the City of Boston.

As with the other health centers, BHHC was founded in response to an invitation from community leaders concerned about a lack of medical services for local residents. Roger H. Sweet, MD, who retired this summer as Medical Director of the centers, recalled the poor state of health care in the Boston neighborhood before the BHHC.

*(Continued on Page 2)*

## *Treatment Program Cuts Diabetes Complications*

THIS SUMMER, when scientists released the results of the largest diabetes treatment study ever undertaken, it put to rest one controversy but may have sparked another.

The 10-year Diabetes Control and Complications Trial (DCCT) produced the first conclusive proof that rigorous control of blood sugar levels can delay and even prevent complications of Type 1 diabetes. Debate continued, however, regarding whether the intensive program — which includes close monitoring of sugar levels and more frequent insulin injections — would be too difficult for most diabetic patients.

While it will take years to answer that question conclusively, data from the DCCT and the experiences of several participants in the trial indicate that, for many, intensive diabetes treatment offers a realistic opportunity to avoid the debilitating and life-threatening complications of their disease.

The MGH was one of 29 sites of the DCCT, sponsored by the National Institute of Diabetes and Digestive and Kidney Diseases. Leading the MGH component was David M. Nathan, MD, Director of Diabetes Clinical Research, who also was editor of all the scientific publications

*(Continued on Page 4)*

*Insulin pump helps patients maintain blood sugar levels.*

INSIDE

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**Zebrafish and Cardiac Development**
*Page 7*

EDITORIAL

## Riches of a More Rewarding Kind

CHARLESTOWN is a one-square-mile Boston neighborhood dominated by a steep hill on which one of the nation's most famous battles took place. In 1968 roughly 17,000 people, many of them Irish-American, lived in its old brick houses rising on Bunker Hill and in its smaller wooden buildings. It was largely a working-class neighborhood, with the second largest housing project in New England. Many lived in poverty, but nearly all had a strong pride in the community.

There were only a few physicians — most looking forward to their approaching retirement — to serve a population with significant health needs. It was in that situation that town leaders asked the MGH to assume the small enclave's large health problems. Thus, 25 years ago this fall, the MGH established its Bunker Hill Health Center.

In the last quarter century, patients have made an estimated 1.25 million visits there. Doctors and nurses climb and descend the hill to make house calls and treat people for everything from AIDS to the flu. They develop relationships with entire families and get to know not only their health problems but also the social conditions which often lead to sickness. As a page 1 article in this issue reports, the MGH subsequently accepted the requests of the people of Chelsea (1972) and Revere (1981) to open health centers in those underserved cities. Chelsea brought the health problems one would expect in a very-low-income community with a large but poor population. Immigrants to Revere have been burdened by diseases such as tuberculosis, not long ago waning in the United States.

Providing medical care in these neighborhood health centers has been neither easy nor monetarily enriching to the MGH. But helping people often desperate for treatment has provided riches of another, more rewarding kind. ■

## —Health centers

*(Continued from Page 1)*

"It was very common for Charlestown children to fail physical examinations for Head Start programs or for young men to fail their draft physicals. Immunization rates were terrible, and dental care was atrocious," he said. "In the preceding ten years there had been a tenfold increase in Charlestown residents coming to the old MGH Emergency Ward for what we now refer to as primary care."

In establishing the BHHC, the MGH did more than open a center where people could see a doctor or nurse if they were ill or injured. Through its community advisory board, the BHHC began an active effort to identify local needs and design programs to meet them.

Services to the schools and to local children have always been a major emphasis at BHHC.

One special program is Camp Bunker Hill, a day camp and after-school program for youngsters with emotional or behavioral problems. During the summer, up to 50 children enjoy recreational activities, in combination with therapeutic and counseling services, at the camp's two locations — Charlestown High School and the Hale Reservation in Westwood. The after-school program, based at a local church, can serve 10 elementary-school youngsters.

When a 1986 study showed that there were more deaths from heart disease in Charlestown than any other Boston

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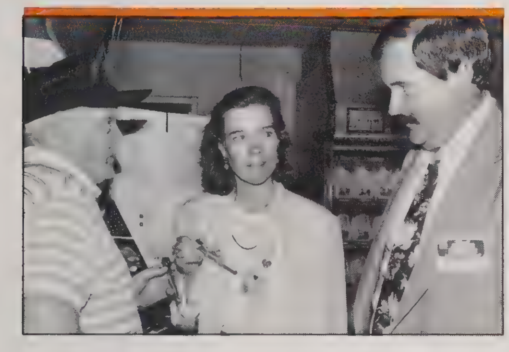
neighborhood, BHHC staff joined forces with community representatives to tackle the problem. One result has been the annual "Charlestown Loves a Healthy Heart" health fair. Held at a local supermarket, the event offers free blood pressure and cholesterol screening, as well as information on heart disease and its risk factors.



*Kris Marchand, BHHC dietitian, discusses the fat content of dairy foods with local residents at the "Charlestown Loves a Healthy Heart" fair.*

The Chelsea center began with a 1972 program to address the needs of that city's children. Demand for services grew so rapidly that the center moved twice during the 70s, eventually locating in the former Chelsea Memorial Hospital in 1978. The late Eleanor Clark, longtime MGH Director of Social Services, helped shape the growth of the Chelsea Memorial Health Center (CHMC).

In serving one of the poorest communities in Massachusetts, the CHMC staff has relied on less formal but still strong relationships with local leaders. Many of the city's elderly residents receive primary care from CHMC physicians or nurse practitioners who visit them in their homes, in elderly housing, or in nursing homes. Because much of the local population speaks Spanish, the great majority of CHMC staff is bilingual. Many of them, in fact, are community residents.

The center operates one of the few 24-hour emergency departments in the metropolitan area that is not located in a hospital building. A satellite clinic at Chelsea High School offers a full range of services to adolescent patients.

Staff members also are involved with several local projects aimed at combating youth violence, addressing issues related to AIDS and HIV infection, and improving public health services.

MGH-Revere Health Associates (RHA) arose from a collaboration between the hospital and an independent physician group. What began as management assistance led to the hospital's being asked to take over the center in 1981. In 1984 the MGH-RHA moved into its current quarters in the Revere Post Office Building.

Although less comprehensive than either the Charlestown or Chelsea centers, the MGH-RHA delivers primary care to a diverse group of patients of all ages and socioeconomic backgrounds. The X-ray, laboratory, and emergency facilities of the Chelsea center are only a few minutes away. As with all three centers, MGH-RHA patients can be referred to specialty caregivers at the main MGH campus.

Close cooperation between the Chelsea and Revere centers extends to several community programs. Chelsea staff have been involved for several years with the Reaching Out to Chelsea Adolescents (ROCA) program. Concern for growing youth delinquency and violence in Revere led Dr. Sweet and other health center staff to encourage an expansion of that program. One of ROCA-Revere's first projects is getting local youth involved in efforts to educate members of their community about tuberculosis.

Cambodian immigrants currently make up more than one-third of the MGH-RHA's patients, and most of them speak little English. The center's three Cambodian interpreters not only translate for patients meeting with caregivers but also act as informal advocates guiding them through the entire health care process.

Both the Revere and Chelsea centers have recently started setting up their own community advisory boards. Mary Leary, Administrative Director of the health centers, notes that the boards not only help the centers target their services to community needs but also bring valuable feedback that can guide future decisions.

"We're going to be closing one of the buildings in Chelsea and are working with the community to investigate temporarily moving some of the programs housed there to another section of town. Long-term we want to address whether the CHMC is in the best location for the community."

Also to be addressed are ways to lessen the inconvenience when Chelsea and Revere patients travel the relatively short distance to the main hospital, which involves a costly cab ride for those without cars. Ms. Leary noted that transportation is the only real barrier between health center patients and the services of the main hospital.

"I think that's one of the things that makes the MGH health centers pretty unique. A lot of the other hospital-licensed community health centers don't have as easy access to the tertiary care center," she said.

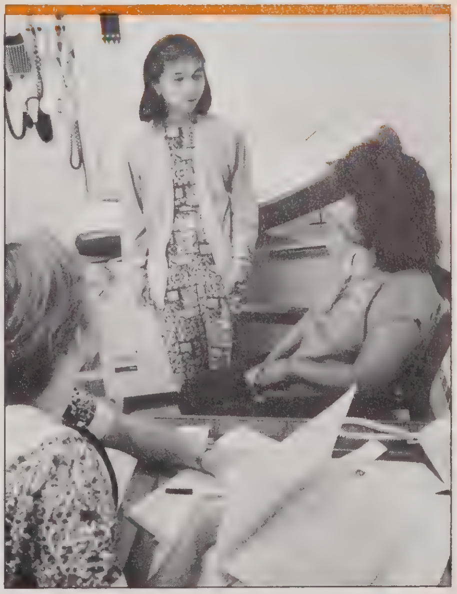
"Another unusual aspect is the centers' multidisciplinary nature," she added. "They really are good models of one-stop shopping for health care."

The close connection between all the health centers and the MGH main campus helps alleviate a common problem in urban areas: finding physicians who will stay in the community. The teaching and research opportunities of the MGH and Harvard Medical School make working at the centers more attractive to primary care physicians.

In addition, the centers are ideal teaching locations for medical students and young physicians interested in primary care and community medicine. The MGH Medicine/Pediatrics residency program has particularly strong ties to the Chelsea and Revere centers (*MGH News*, January-February 1993).

Reflecting on his 25-year involvement with the MGH community health centers, Dr. Sweet noted, "The biggest lesson that anyone could learn from our experience is how important it is to get out there and *listen* to the people you are serving. The community members know what their serious problems are. And when they include public health concerns — from prenatal care, to nutrition, to AIDS education — we can help meet their needs as long as we continue to listen.

"The people who work in the centers, who are out there in the community, are seen as ambassadors of the whole hospital. They really embody the MGH at its best." ■



*At Revere Health Associates, Sokha Pang (standing) helps patient Sary Seang describe her symptoms to Dr. Laura Olson.*

# — Diabetes treatment program

(Continued from Page 1)
produced by the national trial group.

The study focused on Type 1 diabetes — also called insulin-dependent or juvenile diabetes — the more serious of the two primary forms of the illness. Type 1 diabetes develops when the body's immune system destroys the insulin-producing islet cells of the pancreas.

Without insulin, the body cannot properly use the sugar (glucose) from food for growth and energy. Glucose that should be taken into cells is trapped in the bloodstream. Uncontrolled high blood sugar levels can lead to coma and even death.

Insulin allows people with Type 1 diabetes to live healthily for many years but is not a cure. Daily insulin injections — along with careful diet and appropriate exercise — can control levels of blood sugar to a certain extent. But they can only approximate the precise response of a healthy pancreas.

Many patients who survive for years on insulin develop serious complications — including blindness, kidney failure, heart disease, stroke, and damage to nerves and blood vessels. While clinicians suspected that fluctuating blood sugar levels were responsible for complications, that theory had not been proven.

"For years the prejudice of the diabetes community was that maintaining lower blood sugars should make a difference," said Dr. Nathan.

Unfortunately, he explained, the earliest trials of what is now called intensive therapy failed to demonstrate a benefit. In fact, the early studies suggested that intensive therapy was difficult for patients to follow, expensive, and potentially harmful. Patients appeared to be at greater risk for hypoglycemia (low blood sugar) which, when severe, can cause coma.

The early studies had limitations, however. Probably most significant, they examined small groups of patients for only a few years. To study the effects of intensive blood sugar control definitively, the DCCT followed more than 1,400 patients for as long as 10 years.

The trial randomly assigned patients to one of two treatment groups. One group followed a standard course of diabetes treatment while the other pursued a special program designed to keep blood sugar levels under tight control (see box next page).

The results surprised even the most optimistic researchers. Intensive therapy reduced diabetic eye disease (retinopathy) by 76 percent; the development or progression of kidney disease (nephropathy) declined between 35 and 56 percent; and nerve disease (neuropathy) fell by 60 percent.

"Completing the DCCT was crucial to demonstrating that the positive benefits of intensive therapy did indeed outweigh the increased costs and risks," said Dr. Nathan.

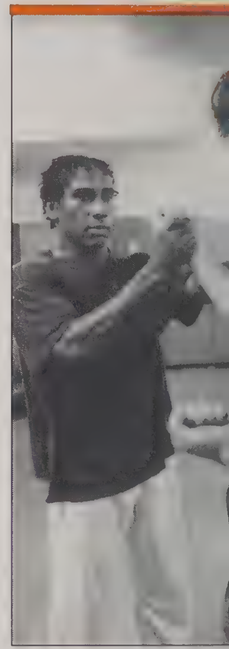
While patients in the intensive treatment group experienced more hypoglycemia, he added, there were relatively few episodes causing injury or requiring hospitalization, and no deaths attributable to hypoglycemia. The added costs of intensive therapy — for monitoring and increased physician, nursing, and dietary care — should be more than compensated by long-term savings.

"Diabetes costs this country about $40 billion a year, with a great fraction of that for treatment of complications," Dr. Nathan said. "Not only will intensive therapy prevent human suffering and lost productivity, but if we effectively implement this treatment in most Type 1 patients, ultimately we will reduce overall costs for diabetes care."

*Left:* *Kati Steinberg checks her blood sugar levels with the assistance of daughters Kelly (left) and Clare.*

***Near right:*** *DCCT participant William Polk works with a student in his Northeastern University martial arts class.*

***Far right:*** *Drs. David Nathan (left) and John Godine*



Dr. Nathan, who also is an associate professor of medicine at Harvard Medical School, noted that intensive therapy is difficult. But he added that patients in the intensive therapy group did remarkably well in meeting their treatment goals.

"They used intensive therapy for 98 percent of the time they were supposed to and maintained glucose levels considerably below those of the conventional treatment group."

Study participant Kati Steinberg, 32, of Lexington found that the DCCT regimen actually fit well into her life.

"When I first heard about the study, I was an undergraduate, leading the disorganized life of a college student. I decided it was not for me. But three years later — when I was married, working, and on a regular schedule — it was the perfect thing to do," she recalled.

Ms. Steinberg entered the DCCT in 1986 at the University of Iowa. When she and her husband moved to Boston in 1988, she continued with the MGH group, under the care of John E. Godine, MD. She believes that her participation in the study really turned around her diabetes control.

"For me, the time before the study was the Stone Age," she said. "Before I started with the DCCT in Iowa, I took one shot in the morning, maybe another at night, and only occasionally did urine tests for blood sugar. I don't know how I survived. I was always thirsty, had headaches, and felt generally lousy. I might as well have been an undiagnosed diabetic."

Not only did Ms. Steinberg feel well throughout her time in the study, she also had two normal pregnancies and now has two healthy daughters.

"I'm the kind of person who does best the more information I have," she explained. "During my pregnancies I was always aware of my sugar levels, and I had three doctors to answer my questions. I probably had no more problems than the average nondiabetic person."

For William Polk, 37, of Roxbury, participation in the DCCT also came at just the right time. He was feeling that his diabetes was out of control and was not satisfied with his care at another Boston hospital.

In frustration he tried to adjust his insulin dosages on his own, and although he started to feel better, he also had several serious hypoglycemic reactions.

"The only time I felt good was when I was working out," said Mr. Polk, who is a martial arts instructor. "Otherwise I was constantly getting sick — when anyone sneezed, I got a cold. And looking back now, I realize I didn't know what it was like to feel really well."

After seeing a newspaper item about the DCCT, he enrolled in the MGH study group. "Initially I feared being in the experimental group, I didn't want to take more than one shot a day. But when I found out that I'd been assigned to it, I said I'd do it anyway."

Instead he found that the self-monitoring and personal responsibility inherent in intensive therapy fit perfectly with his desire to take control of his condition.

"This is my life now; I really enjoyed learning more about myself and my diabetes. When you don't understand about adjusting insulin and about what's right for you, that's when you have a hard time."

***With the DCCT results now supporting intensive therapy, the MGH has established a new Diabetes Treatment and Research Center to make the program's benefits available to any MGH diabetes patient.***

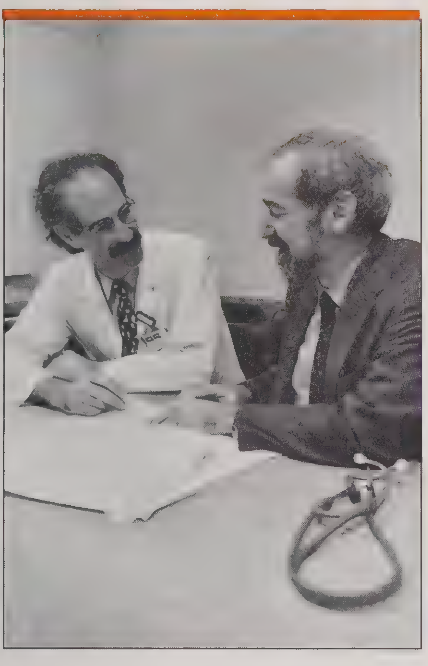
Although the DCCT studied Type 1 diabetes, it is expected that an adapted version of the treatment will benefit patients with Type 2 diabetes, the more common but less severe form.

Dr. Nathan noted that several elements of intensive therapy — particularly close blood sugar monitoring and more frequent insulin injections — have been phased in over recent years at the MGH and other centers. Now permanent teams of physicians, nurses, and dietitians are forming to provide education and support to patients embarking on the complete program.

"The resources we made available to the intensive therapy group in the DCCT — particularly the expert, multidisciplinary teams — were a major reason the patients were able to accomplish the therapy so safely and effectively," Dr. Nathan said. "That support is essential to a broad-scale application of intensive therapy."

He adds that the DCCT results also support the importance of research efforts to develop even better methods of controlling blood sugar levels. These include better oral drugs to improve the utilization of insulin in Type 2 diabetes; implantable insulin pumps that could automatically adjust dosage in response to blood sugar; and transplantation of pancreas islet cells. All these concepts are being pursued at the MGH (*MGH News*, March 1992).

"With the evidence provided by the DCCT," said Dr. Nathan, "there is even greater motivation to develop these new methods because we know we can improve the long-term outlook for our patients." ■



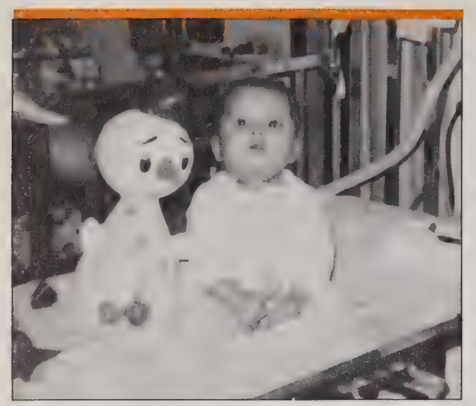
## Intensive Therapy Requires Rigorous Regimen

Participants in the Diabetes Control and Complications Trial were divided into two groups. The first followed a conventional Type 1 diabetes treatment plan, which involved daily blood sugar tests, insulin injections once or twice a day, a standard nutrition and exercise program, and a visit every three months with the clinic team.

After an initial hospital stay to start them on the program, the intensive therapy group tested their blood sugar levels four or more times a day. Testing was accomplished with a pinprick of blood and special equipment to analyze the samples.

Intensive therapy patients also used either an insulin pump — which provides a constant infusion of insulin, along with larger doses before meals — or took three or more injections daily. Closer monitoring allowed frequent dosage adjustments to compensate for changes in food intake or exercise.

Participants met monthly with a physician, nurse, and dietitian to track their progress and help make adjustments in their program. ■



# For 20 Years, Adelaide Has Led the Way

Adelaide Jorge is a pioneer. The quiet young woman from Somerville may not appear remarkable, but every accomplishment of her life has paved the way for scores of other children.

Twenty years ago, Adelaide was the first child diagnosed with a rare condition called Congenital Central Hypoventilation Syndrome (CCHS), a neurologic disorder that affects breathing. Today she is the first CCHS child to live two decades.

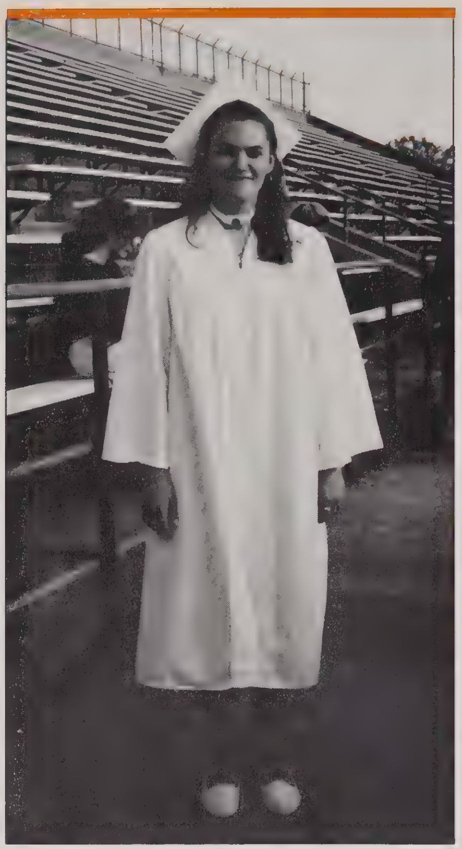
Children with CCHS are fine when they are awake, but as they sleep, their breathing becomes shallow. Their bodies do not receive sufficient oxygen or eliminate enough carbon dioxide ($CO_2$). They may turn blue from lack of oxygen and stop breathing altogether.

Adelaide had trouble breathing soon after her 1973 birth at Cambridge Hospital. She was transferred to the MGH where she came under the care of Daniel C. Shannon, MD, who now is Chief of the MGH Pediatric Pulmonary Unit.

Earlier in his career Dr. Shannon had seen adults with a condition that usually developed after a serious respiratory illness. Their symptoms of fatigue, difficulty awakening, and headaches were traced to insufficient breathing while asleep.

He had also read reports of an infant who died after several months of similar symptoms. Theorizing that that child and Adelaide both had an inborn version of the adult syndrome, he began to devise a treatment program for her.

Initially Adelaide slept in an iron lung. This metal device encases the whole body from the neck down. By applying negative pressure (like the suction of a vacuum cleaner) to the torso, the iron lung expands the lungs. Being elastic, the lungs empty themselves when pressure is released.



*As an infant (upper left) Adelaide Jorge was frequently admitted to the MGH for her breathing problems. Last year she graduated from Somerville High School.*

Adelaide went home with the iron lung. But the device proved inadequate, and within months she was back in the MGH. An opening (tracheostomy) was made directly into her windpipe to allow air to be pumped in and out by a positive-pressure ventilator.

Although they spoke little English at the time, Adelaide's parents learned how to take care of their daughter at home.

Maria Jorge, her mother, recalled that the family knew there were many unanswered questions about Adelaide's illness. "The first years were hard because there was so much we didn't know. There was nobody to call except Dr. Shannon, and he was learning too because it was something new. But we were able to take care of her at home, and everything turned out fine."

As Adelaide grew older, she — and other children subsequently diagnosed with CCHS — began to answer some of the questions about what children with the disease could and could not do.

An initial obstacle was learning to speak. Because a tracheostomy enters the windpipe below the larynx (voicebox), there usually is not enough air passing through the vocal cords to permit speech.

But Adelaide discovered a technique also used by other CCHS children — closing the tracheostomy with her finger or by dropping her chin to compress her neck — and began to speak on her own. Today she and others use a plastic plug or valve (developed by Roland D. Eavey, MD, of the Mass. Eye and Ear Infirmary and Dr. Shannon) to close off the opening when it is not used for ventilation.

Since CCHS children do not outgrow their condition, they continue to need breathing support at night. While most continue with a ventilator, other techniques have been tried.

One involves electrical stimulation of the phrenic nerve, which helps control the diaphragm, via implanted wires similar to those used in a cardiac pacemaker. But that procedure still requires a tracheostomy, the aspect of ventilator care that children and their parents most object to.

"The neuroregulatory problem that characterizes CCHS affects not only the diaphragm but also the laryngeal muscles," Dr. Shannon explained. "To successfully breath, you normally send signals to your larynx that tell the vocal cords to open a fraction of a second before the diaphragm contracts. These signals are missing in CCHS, so there is an obstruction that must be bypassed with a tracheostomy."

Another strategy involves a mask that fits over the nose and mouth, connected to a ventilator that pushes in enough air to separate the vocal cords. Although that could eliminate the need for a tracheostomy, Dr. Shannon's patients who tried the mask did not like it and chose to go back to standard ventilation.

As Adelaide and other CCHS children treated at the MGH have grown older, Dr. Shannon and colleagues at the Harvard School of Public Health have been able to address other questions through research studies. Some of their recent findings upset previous assumptions about respiratory control and produced intriguing hints about the basis of CCHS.

Physicians believed the increased ventilation of the lungs that occurs with exercise is caused by changes in oxygen and $CO_2$ levels in the blood. Children with CCHS, however, lack chemical receptors in the brain that sense these changes. Therefore it was expected that they would not change their breathing as they exercised. ***But tests of CCHS children showed they respond to exercise just as normal children do, by breathing enough to support the***

***increased demand for oxygen. That result implies that another mechanism must be involved in normal exercise-related breath control.***

The studies also confirmed that those with CCHS do not feel the normal warning sign of "breathlessness" if they inhale $CO_2$-rich air or hold their breath.

"If these children learn to swim — and many of them do — they have to keep track of how long they stay underwater and come up for a breath," said Dr. Shannon, who also is professor of pediatrics at Harvard Medical School and a professor in the Harvard/MIT Health Sciences and Technology Program.

Other interesting observations about CCHS children are: their heart rates do not show the constant variation that normally occurs with each breath; the pupils (colored portion) of their eyes respond abnormally to bright light; and they lack a cough reflex.

All of these differences point to the parasympathetic branch of the autonomic nervous system that controls all involuntary bodily functions. If the primary defect that underlies these problems can ever be identified — it is suspected to involve chemicals that control the parasympathetic system — it may be possible to correct it with medications.

Last summer Adelaide graduated from high school, in spite of some learning problems that may result from lack of oxygen in her early years. She now works part time in a local department store and hopes someday to marry and have a home of her own.

Her mother warmly expresses appreciation of the support her family received from the MGH over the years — particularly from Dr. Shannon and from Karen Sullivan, RN, in the Pulmonary Lab. But she speaks with pride of her daughter's own accomplishments.

"Adelaide does her job very well; she's only called in sick once. It takes her a little longer to learn, but she finished high school with Bs and Cs. Everything she has done she did on her own!" ■

# Zebrafish Provide Window on Cardiac Development

A TINY TROPICAL FISH is helping scientists decipher genetic signals that direct the earliest stages of development, the process by which the fertilized egg grows into a complete, complex organism. By studying the inch-long zebrafish, researchers at the MGH Cardiovascular Research Center (CVRC) are pinpointing genes that play critical roles in development of the heart and other organs.

Mark C. Fishman, MD — director of the CVRC — explained that while much had been known about the large-scale development of the cardiovascular system, there was little understanding about the genetic underpinnings of that process.

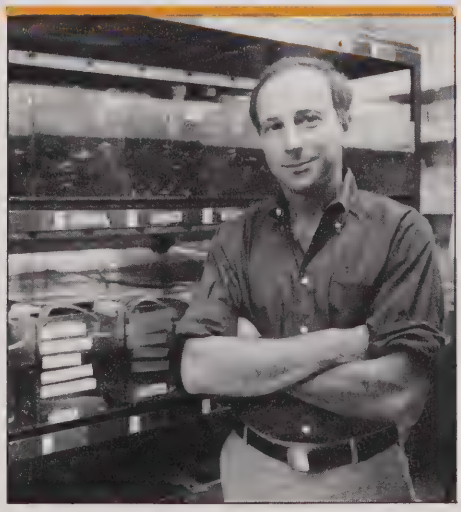
"The cellular and molecular aspects of cardiovascular biology have lagged behind other fields, such as cancer biology," he said. "In starting the CVRC we wanted not just to let cardiovascular biology catch up with the rest of biology but also make it a leader in basic science that would be very applicable to patient care."

Much of what has been learned about how particular genes control development comes from intricate studies of worms and fruitflies. While those studies have produced important information, their relevance to human organ development is limited. Such animals don't even have the kind of cardiovascular systems found in mammals and other vertebrates (animals with a backbone).

Mice have also been subjects of genetic research. It is now possible to inactivate certain genes in mice and to identify the role of those genes by observing alterations in the affected animals. Several CVRC researchers — including Paul Huang, MD, and En Li, PhD — are working with these techniques.

But genetic changes or mutations affecting such vital organs as the heart often prevent the animal from surviving until birth — or even past the first stages of development.

"The heart is a critical organ — in humans it begins to function at three and a half weeks of gestation. If there was an important defect in early development of the heart, the embryo probably wouldn't make it," Dr. Fishman said. In mice and other mammals, such an embryo might be absorbed by the mother's body.



*Dr. Mark Fishman*

"Even though about 1 in 100 human births is complicated by a congenital heart defect, that's only the tip of the iceberg," he added. "It's very likely that we don't even know what most genetic heart defects are. The ones that make it to birth are — by definition — less serious than those that don't survive."

One advantage of the zebrafish is that development can be observed from the earliest stages. The eggs are fertilized outside the body, and both the eggs and the embryos are transparent. They also grow quickly; the heart is functioning 24 hours after fertilization.

Put simply, the strategy followed by CVRC researchers is to induce genetic mutations in the fish, observe the effects on offspring, and find the gene responsible for the changes through standard genetic mapping techniques. Accomplishing that task, however, is extremely complex. The techniques were developed by CVRC scientist Wolfgang Driever, PhD, based on his earlier studies of fruitflies.

As with other higher animals, a zebrafish inherits two copies of each chromosome (except for the X and Y chromosomes which determine sex), one from each parent. To produce fish that show the effects of the mutations requires careful crossbreeding of three generations of offspring (see box on page 8).

Dr. Driever, Dr. Fishman, and their colleagues microscopically examine the third-generation embryos at several stages of development to search for abnormalities. In addition to genes affecting the cardiovascular system, the groups have found genes involved with several other organs.

Dr. Driever noted that identifying the

*(Concluded on Page 8)*

## — Zebrafish

*(Concluded from Page 7)*

gene responsible for a mutation involves the same techniques used by MGH researchers to find genes for Huntington's disease and other significant genetic conditions (*MGH News*, April 1993).

***"Mapping the Huntington's gene required information from 7,000 related people in Venezuela and took many years," he said. "We can make a family of 10,000 fish within three months."***

In terms of the heart, several genes affecting development have already been identified. Mutations have produced embryos lacking a heart chamber, lacking a valve, with irregular heartbeats, and even with no heartbeat at all.

***"What is quite interesting," Dr. Fishman said, "is the fact that we actually can do this. It was possible that the genes important to forming the heart were so crucial to earlier stages of development that we'd never see any specific organ mutants at all. But it turns out that you can get many lesions that are very specific to the heart. We've really defined a whole new set of genetic diseases here."***

Dr. Fishman adds that his group's overall goal is very ambitious — to define every gene involved in forming the heart. While the project is off to a promising start, he anticipates its completion may take 10 years or more.

"No one else is trying to do this in vertebrates," he said. "With the concepts and techniques Wolfgang has developed, it may be possible to 'saturate' the genome [find every possible lethal mutation that affects early development]."

One can only guess about the patient care impact of this work — and the work of CVRC scientists studying genetic factors in mice and humans. While congenital heart disease appears the most immediate application, most cardiovascular diseases run in families, indicating a genetic component.

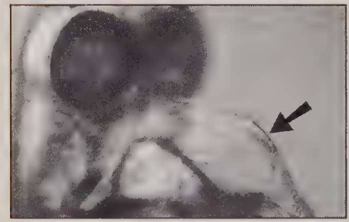
"We are entering an era of potential gene therapy, and there's no telling what problems we may be able to solve," said Dr. Fishman, who also is associate professor of medicine at Harvard Medical School.

"Some may say there's no way we're going to find all the genes for congenital heart disease, much less cure them. But if people had taken that kind of attitude to the state of the art 50 years ago, they never would have developed congenital heart surgery at that time. I don't think it's a complete fantasy that — in 10 to 20 years — gene therapy for heart disease might be approachable." ■

## *Painstaking Process Reveals Effects of Mutations*

To PRODUCE a population of zebrafish that show the effects of genetic mutations, MGH researchers begin by treating zebrafish sperm with chemicals that alter genetic material. When that sperm fertilizes normal eggs, each offspring inherits only one copy of any mutated gene.

In most instances that single altered gene would not be enough to override the normal parent's gene and change the animal's physical form. In addition, current techniques produce random mutations. Different genes are changed in each sperm, so that each offspring carries a unique mutation.



*The mutated heart (arrow) of this 48-hour-old zebrafish embryo is enlarged and does not beat. At upper left the head and eye can be seen.*

When these first-generation fish are mated with normal fish, half of the offspring of each pair will inherit one copy of the mutant parent's altered gene and one copy of the normal gene. Among the offspring of each pair, only one specific mutation can be inherited.

Finally second-generation fish are mated with siblings — offspring of the same set of parents — to produce fish that may inherit the mutated gene from both parents and thus would not have a normal, functioning copy of the gene. It is in this third generation that the physical changes caused by a mutation appear. ■

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# Bringing Children Back From Serious Injury

WHEN A CHILD or adolescent is seriously injured, everyone's first concern is his or her survival. As a Level 1 regional trauma center, the MGH has the emergency staff, specialized surgeons, intensive care nurses, and other support services to give the most seriously injured children (as well as adults) the best possible chance of recovering.

Once the child's most acute needs are met, however, another set of problems can crop up: problems related to long-term effects of injuries or psychological stresses on patients and their families. To help anticipate and deal with those problems, last year a Pediatric Trauma Rehabilitation Team was established within the MGH Children's Service, the hospital's pediatric department.

"We've become excellent at saving injured children who might not have been saved before and reducing the permanent effects of their injuries," says Robert Wharton, MD, an MGH pediatrician who is heading the team. "It seemed to make sense to examine whether we're also meeting their other needs, both during their hospital stay and after they return home."

What Dr. Wharton and his colleagues found, upon examination of standard hospital practices, was that pediatricians were rarely involved in the care of injured children. Instead, their treatment was entirely supervised by the pediatric surgeons who repaired their injuries. What was less attended to, he explained, was the broader perspective on children's needs that pediatricians can provide.

"Our surgeons do their jobs exceedingly well, but pediatricians have specialized training and experience in child develop-

*(Continued on Page 6)*

# *Dr. Frigoletto to Lead MGH Obstetrics Division*

IN A MAJOR STEP towards the reintroduction of obstetrics at the MGH, Frederic D. Frigoletto, Jr., MD, has been named Chief of Obstetrics in the Vincent Memorial Obstetrics/Gynecology Service, the women's care division of the hospital.

Dr. Frigoletto previously was Chief of Obstetrics and Vice Chairman of Obstetrics and Gynecology at Brigham and Women's Hospital in Boston. "He is one of this country's most distinguished leaders in obstetrics and has an outstanding reputation for patient care," said Isaac Schiff, MD, Chief of the MGH-Vincent Memorial Obstetrics/Gynecology Service.

During his 30-year career, Dr. Frigoletto also has been a leader in several research areas, particularly the use of ultrasound (images made with high-frequency sound waves) to diagnose and guide the treatment of certain birth defects. Earlier this year he coauthored a study that showed routine ultrasound screening was not beneficial in low-risk pregnancies.

***The new position is "an unbelievable opportunity," said Dr. Frigoletto. "I know of no one in my profession who***

*(Continued on Page 2)*

*In an innovative program, the staff of the MGH Emergency Department has some special new colleagues — stuffed animals to help comfort frightened, injured children. Here nurses Suzanne O'Connor and Cindy Nigro hold some of their fuzzy friends. (See story, page 4.)*

## INSIDE

**Simple Comforts for Injured Children**
*Page 4*

**A Chemical Key**
*Page 7*

EDITORIAL

# Sometimes the Best Things in Life *Are* Free

IN THE HIGH TECHNOLOGY WORLD of health care, sometimes it is the small, inexpensive things which make the difference. The problem in this instance was at the MGH pediatric trauma center. The nurses of the MGH Children's Service choose to work in pediatrics because of a special bond with and desire to help the young. In a pediatric trauma center, however, the nurses generally have to cause the already hysterical youngsters additional pain by giving shots, dressing wounds, etc.

Enter Suzanne O'Connor, RN. A psychiatric clinical nurse specialist, Ms. O'Connor felt determined to resolve this plight of patient and nurse when she read about police officers in a Massachusetts community. They faced similar concerns when summoned to quell domestic disturbances or in child abuse cases. When the police needed to remove the child from such a home, they found they could placate the unhappy young one by letting the youngster play with a fuzzy toy they kept in the cruiser for such purposes.

Ms. O'Connor wondered if the little fuzzy might have a similar calming effect on traumatized children treated at the hospital's pediatric trauma center. With the help of the MGH Police and Security officers, she soon found out. The officers brought in stuffed animals from home to donate to the children.

The very first chance to test the fuzzies came in the person of a terrified youngster severely injured in an automobile accident. The child's mother was herself being treated in the adult trauma center for a serious back injury. Not only was the mother unable to go to the pediatric section but she also blamed herself for causing the accident. A dinosaur, chosen by the mother from a number of fuzzy animals shown her by Ms. O'Connor, had the desired effect. In minutes the child turned from screams to calm as he clutched the stuffed toy Ms. O'Connor introduced as coming from the mother.

The complete story of the fuzzies is told in a page 4 article. In a teaching hospital known for its technology costing tens of millions of dollars, it is refreshing to observe how inexpensively some solutions come. ■

## —Dr. Frigoletto

*(Continued from Page 1)*

***has had the opportunity to start a totally new obstetrical service, especially at a world-class institution like the MGH."***

Obstetrics has been the "missing" service at the MGH for about 40 years. In 1991, the decision was made to reinstate obstetrics at the MGH (*MGH News*, January-February 1992), beginning next year.

"The MGH cannot be a full-service hospital until it offers obstetrics," explained Dr. Schiff. "We are the neighborhood hospital for patients from several areas; but we must send them elsewhere to have their babies. Many women who come here for specialty care — especially the services of our infertility unit — are frustrated when they cannot continue with their MGH doctors during pregnancy."

Dr. Frigoletto added that many patients are first introduced to an institution through its obstetric service. "When women have their babies at a hospital, they often return there for their child's care and for other services their families may need."

The obstetric service will be located in the hospital's newest building, being completed as the final phase in a 10-year inpatient facility renovation program. Outmoded patient care rooms are being replaced, with an overall reduction in patient beds. (A portion of this 14-story building is remaining vacant while the hospital determines the best use for the space in today's changing health-care environment. But floors housing several

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PHOTOGRAPHS: Page 1, 3 (upper), 6, 7, Susan McGreevey; page 3 (lower) Wendy Matarazzo.

essential services — including obstetrics — are being completed on schedule.)

Expectant mothers will be able to register for prenatal care at the MGH next summer, and labor and delivery facilities should be ready for patients in November 1994. The unit will include 21 inpatient beds, 11 labor/delivery/recovery rooms, and 2 rooms for caesarean sections. Eventually the division will be able to handle 2,000 deliveries a year.

*Dr. Frederic Frigoletto*

Care will be provided by a team consisting of both obstetricians specializing in high-risk pregnancies and midwives, certified professionals (usually nurses) who provide prenatal care and can deliver babies when no problems are anticipated. Dr. Frigoletto noted that such a system offers patients maximum choice.

"We anticipate that most women with no apparent complications will select midwifery. Some will prefer a doctor, and they can choose one of the obstetricians, even though they are low-risk patients," he said.

***Dr. Frigoletto added that he regards obstetricians and midwives as cooperative colleagues, rather than as competitors. "My conviction is that the two professions are much more similar than dissimilar. There should not be any barriers between the two.***

"Indeed, there often needs to be overlap. When a patient who starts in a low-risk category develops a problem during her pregnancy, she can transfer to the care of a high-risk obstetrician and maintain contact with the midwife who initiated her care."

Over the coming months, Dr. Frigoletto will be assembling the team of specialists who will staff the obstetric division. "Although the service and the facilities will be new, the team will be a group of seasoned professionals who have worked together for a long time," he said.

Among the members of Dr. Frigoletto's Brigham and Women's team who will be joining the MGH staff is Beryl R. Benacerraf, MD, an MGH-trained radiologist who will direct the program in obstetric ultrasound, co-sponsored by the Department of Radiology and the obstetrics/gynecology service. Her colleagues Allan Nadel, MD, and Bryann S. Bromley, MD, will also join the MGH/Vincent group. In addition, Michael F. Greene, MD, will join the group as Director of Maternal/Fetal Medicine, along with his colleague Robert Blatman, MD.

Dr. Frigoletto's research has focused on prenatal diagnosis and treatment of birth defects and other problems affecting infants. Early in his career he participated in some of the first trials of intrauterine blood transfusions to treat RH negative disease — a potentially fatal condition caused by a blood-group incompatibility between the mother and child. New treatments have greatly reduced this disorder, but some techniques developed have found wider application.

"The availability of real-time [instantaneous] ultrasound markedly improved our ability to safely transfuse a moving fetus," he said. "And that has opened the window to diagnose and treat conditions that weren't even in our minds when we started."

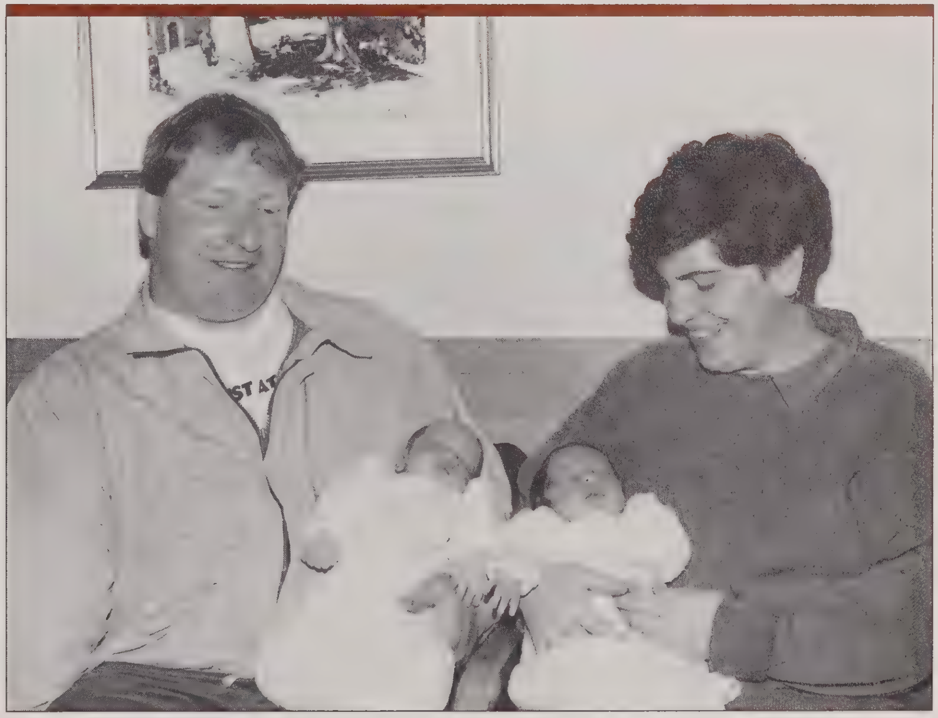
One such condition is obstruction of a fetus's bladder. Without treatment, urine backs up into the kidneys and destroys the organs. Ultrasound can diagnose the problem and, in appropriate circumstances, guide surgeons operating to drain the unborn child's bladder and preserve the kidneys.

Dr. Frigoletto added, "The technology also allows us to sample fetal blood directly for DNA or chromosomal studies to diagnose genetic illness. In the future, I expect it will be the basis of gene therapies for these diseases."

Dr. Frigoletto's most recent study showed that the common practice of routine ultrasound screening of all pregnancies — as opposed to when there is indication of a possible problem — does not appear to prevent disability or death of the infant.

"As a diagnostic tool, ultrasound is very powerful. It's easy to get fooled into thinking that if something is a good diagnostic tool it will be a great screening tool. And before you know it, we're spending millions of dollars a year on something with no proven efficacy," he explained.

Dr. Frigoletto is a *cum laude* graduate of Boston University School of Medicine. He completed his surgical and obstetric training at Boston City Hospital and Boston Hospital for Woman, where he joined the staff in 1967. Since 1986 he has been the William Lambert Richardson Professor of Obstetrics at Harvard Medical School. ■


*Matthew Fee and Sheila Carroll-Fee hold their month-old twins Ruby (left) and Henry. The first infants successfully conceived through the MGH In-Vitro Fertilization (IVF) program, the babies were born in September at Boston's Beth Israel Hospital. Next fall, when new obstetrics facilities are complete, parents like the Fees will be able to have their babies at the MGH.*

# Simple Comfort Can Ease Child's Fear

INJURED AND IN PAIN, a young child arrives at the MGH Emergency Department in a wailing ambulance. In a brightly lit, noisy room the confused, terrified child is surrounded by strangers intent on treating possibly life-threatening injuries. The parents — who may also have been injured in the same accident that sent the child to the hospital — are nowhere to be seen.

In the midst of this scene appears a nurse with a simple, yet potent form of comfort — a stuffed animal or doll that can be the child's special friend throughout his or her hospital stay. In a program started in the summer of 1992, MGH pediatric emergency nurses have given almost 1,000 toys to children treated in the Emergency Department (ED).

***The MGH is believed to be the first hospital in the nation to routinely give stuffed animals to frightened children in the emergency room. Hospital staff also use the stuffed animals to help prepare children for what will happen to them — putting an oxygen mask on a teddy bear or bandaging a toy bunny's leg.***

Suzanne O'Connor, RN, MS, an MGH psychiatric clinical nurse specialist, came up with the idea after reading about policemen in some communities who successfully used stuffed teddy bears to calm lost or hurt children.

"No one is prepared for an emergency," she explained. "One moment a child may be riding in a car. The next thing she knows, she is in the emergency room." Nine out of ten children admitted to the department are alert and aware of what is happening to them.

"At what may be the most frightening moment of a child's life, a stuffed animal can provide an opportunity to share the intense experience and be distracted and comforted by their new companion," Ms. O'Connor added.

The solace children receive from these toys can actually assist in their care. The first child to benefit from the program was a six-year-old boy brought in with a fractured skull and jaw after an automobile accident. Every time he cried or yelled, his bleeding would intensify.

His mother, injured in the same accident, was immobilized on a stretcher in the adult emergency area. She was anxious about her son and felt guilty that she could not be with him. Ms. O'Connor brought her a selection of toys, and she choose a dinosaur — the boy's favorite animal — to send to the child.

Ms. O'Connor told the boy that his mother wanted him to hold the toy and would be with him as soon as she could. Clutching his new friend, the child soon fell asleep.

Offering the toys also helps nurses establish trust and begin relating on a positive level with a child, often before they must perform a painful examination or procedure. The animals can open up communication between ED staff and children whose parents may not yet have arrived at the hospital.

Stuffed animals may be the only way to comfort very young children who do not yet have language skills. They also bring a universal message of solace to non-English-speaking children.

Added Ann Turner, RN, an ED nurse who is a member of the Pediatric Nursing Committee, "Kids are always touched when they receive a present, especially during a procedure when the parent must leave the room. Holding on to the toy may diminish the child's fear when he is alone."

The fact that children can choose their own animal, noted Ms. O'Connor, gives them something over which they have a bit of control in an otherwise overwhelming situation.

"We present them with several to pick from," she said. "They don't necessarily choose the biggest or the prettiest. They're just delighted to have a choice."

The use of toys in the hospital is not new. For many years members of the Child Life Department and nurses in the MGH Children's Service have used special dolls to explain medical procedures to children and give them the opportunity to act out their experiences (*MGH News*, December 1992).

But the MGH is believed to be the first hospital in the nation to routinely give stuffed animals to frightened children in the emergency room. As with the educational dolls, hospital staff also use the stuffed animals to help prepare children for what will happen to them — putting an oxygen mask on a teddy bear or bandaging a toy bunny's leg.

In a letter sent to the ED staff last fall, David Zaleske, MD, Chief of the MGH Pediatric Orthopaedic Service, described how useful an animal was in explaining emergency surgery to one of his young patients.

"I think this could prove to be very satisfying to all children as a comfort measure and a teaching tool. As you know, the emergency room can be very overwhelming and a scary place to a big person, let alone a child," he wrote.

George P. Baker, MD, MGH Associate General Director for Professional Relations, recalled a similar situation when his granddaughter was brought to the MGH with a seriously broken leg.

"The anesthesiologist and residents used [the bunny] to explain what was in store for her, and once she awoke on the pediatric floor in a full body cast, there was her bunny in exactly the same 'get-up'."

All of the toys — which the children may take home with them — have been donated to the program. The MGH Police and Security Department donated the first group, ED staff members frequently make contributions, and the Ladies Visiting Committee has established a fund to replenish the supply when necessary.

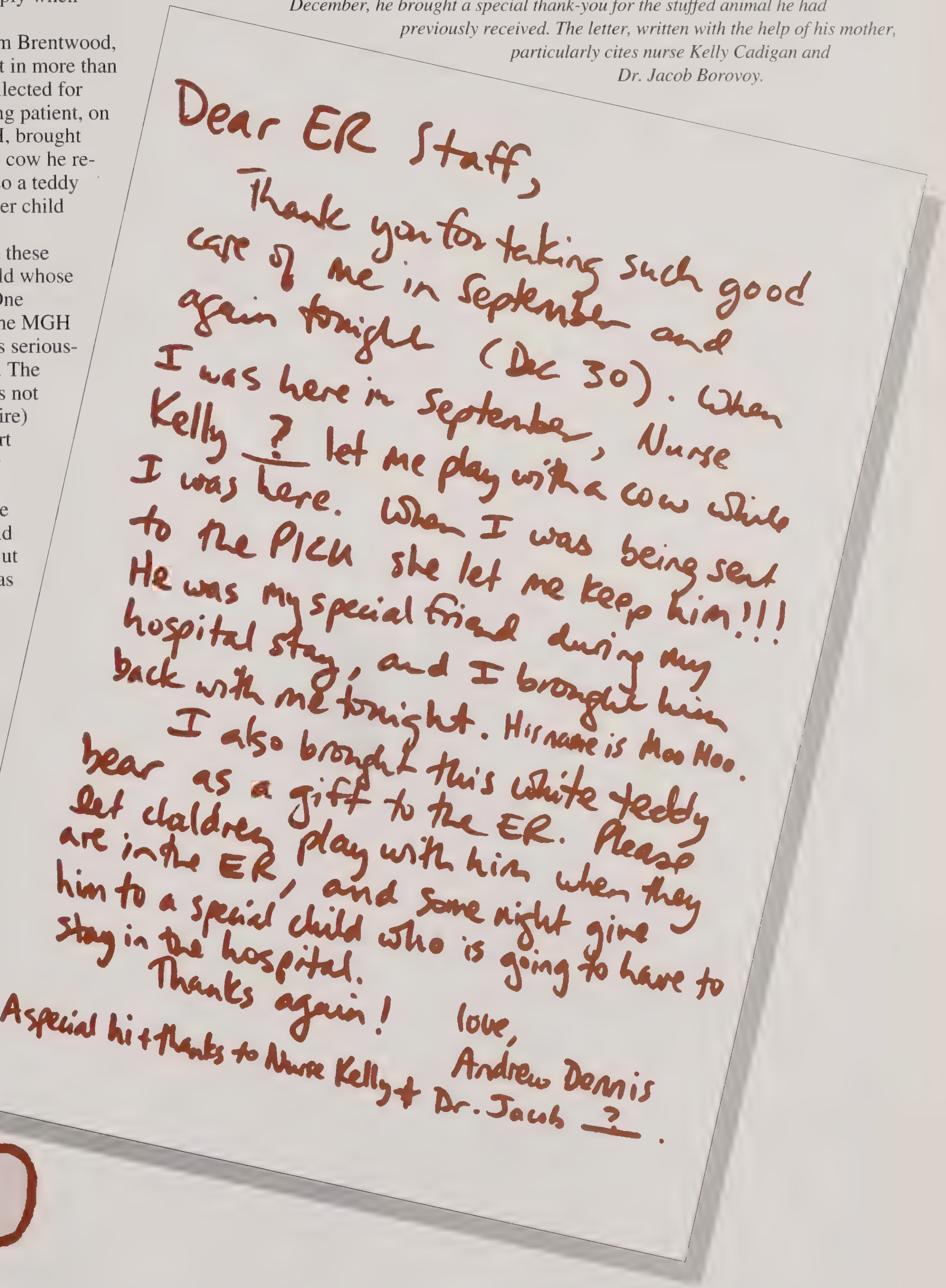
A sixth-grade class from Brentwood, New Hampshire, brought in more than 200 animals they had collected for MGH patients. One young patient, on a return visit to the MGH, brought back not only the stuffed cow he received previously but also a teddy bear to be given to another child (see letter).

Sometimes the comfort these toys bring can help a child whose needs are not physical. One 7-year-old girl came to the MGH with her mother, who was seriously burned in a house fire. The uninjured child (who was not home at the time of the fire) knew her mother was hurt and waited anxiously for news of her condition.

When an ED nurse gave her a stuffed toy, the child clutched it and smiled. But later when the mother was transferred from the ED to the MGH Burn Unit, the girl asked the nurse to give the toy to her mother.

"She needs it more right now," the child said. ■

*When 4-year-old Andrew Dennis made a return visit to the MGH Emergency Department last December, he brought a special thank-you for the stuffed animal he had previously received. The letter, written with the help of his mother, particularly cites nurse Kelly Cadigan and Dr. Jacob Borovoy.*



Dear ER Staff,

Thank you for taking such good care of me in September and again tonight (Dec 30). When I was here in September, Nurse Kelly ? let me play with a cow while I was here. When I was being sent to the PICU she let me keep him!!! He was my special friend during my hospital stay, and I brought him back with me tonight. His name is Moo Moo.

I also brought this white teddy bear as a gift to the ER. Please let children play with him when they are in the ER, and some night give him to a special child who is going to have to stay in the hospital.

Thanks again!

love,

Andrew Dennis

A special hi + thanks to Nurse Kelly + Dr. Jacob ? .

# — Seriously injured children

*(Concluded from Page 1)*
ment and family dynamics that allow them to recognize potential problems that might not be noticed otherwise," he said.

These can include a loss of intellectual ability or emotional control from a head injury, the impact of caring for an injured child on other family members, an inability to participate in activities — such as sports — that were important to the child's sense of self, and communication with the family pediatrician.

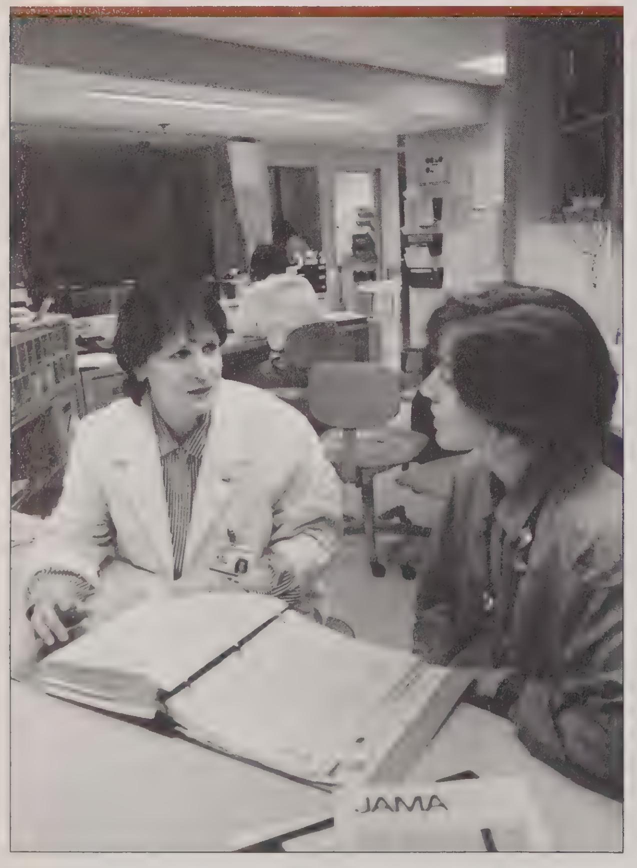
In addition to Dr. Wharton, the team includes Elizabeth Dooling, MD, pediatric neurologist; Alice Gervasini, RN, MS, trauma coordinator; Caren Harris, RN, clinical teacher; Denise Lozowski, RN, MSN, clinical nurse specialist in pediatrics; and representatives from the Social Work and the Speech, Physical, and Occupational Therapy Departments.

As trauma coordinator for the entire hospital, Ms. Gervasini keeps track of all injured patients admitted to the hospital. Children with specific, serious injuries — head injury or prolonged loss of consciousness, spinal cord injury, multiple trauma, or pre-existing medical problems — are referred to the Trauma Rehab Team.

Members of the team regularly visit with the child and the parents in the context of their individual specialties, and they get together weekly to compare notes on each child's progress. Sometimes the picture formed by the pieces each member contributes shows a condition that might otherwise have been missed.

When a child has a head injury, there may be aftereffects involving vision, hearing, language, thinking ability, attention span, and emotional control — not immediately apparent in the less-demanding environment of a hospital. Adolescents, in particular, may minimize such problems in an effort to be as "normal" as possible. Little clues spotted by individual team members can keep these children from slipping through the cracks.

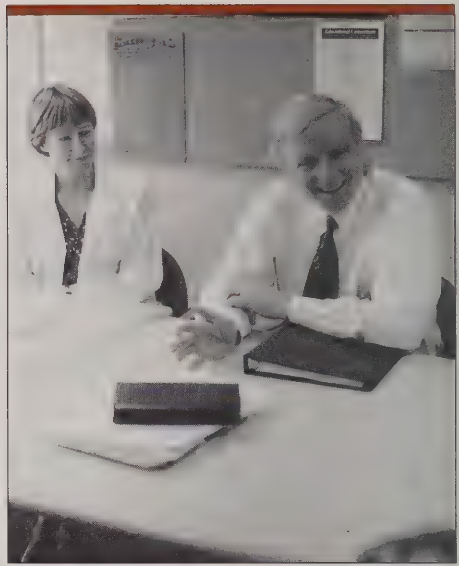
Often these clues show up as problems with language — difficulty answering questions or organizing and discussing thoughts — uncovered through screenings done by speech-language pathologists. Team member Alison Moore, MS, CCC/SLP, noted that knowing how the typical stages of head injury are manifested in a patient's ability to communicate helps to diagnose problems and track recovery.


*Alice Gervasini and Caren Harris discuss a young trauma patient's progress in the Pediatric Intensive Care Unit.*

"We want to see that they are making progress and educate their parents as to what to expect for the future," she said.

Working closely with the family helps team members gain a better understanding of the child's normal behavior and any additional problems that may complicate recovery. They also help parents cope with unexpected situations that can occur during or after a hospital stay.

Dr. Dooling explained that a child who appears to have recovered physically from a head injury may display trouble concentrating, irritability, emotional outbursts, and impulsive, even violent behavior that may not show up until he or she returns to school.


*Denise Lozowski and Dr. Robert Wharton at a weekly meeting of the Pediatric Trauma Rehabilitation Team.*

"Parents can feel so frustrated," she said. "They know they should be grateful their child is alive and has recovered, but it may seem that the child is a different person. Preparing the family for these possible changes and providing continuing support is really necessary."

This kind of support can come from MGH social workers during the hospital stay, from the family pediatrician in consultation with the MGH team, or from other resources in the communities. The Trauma Rehab Team's goal is to make sure that no child gets lost in the system, even when problems appear weeks or months later.

Meeting that goal includes helping families plan for the child's discharge — whether to the home or a rehabilitation hospital — and working with schools to plan for the child's return.

The skills of the team members can also help other MGH staff better manage their patients' needs. For example, many 15- to 18-year-olds are cared for by one of the MGH adult patient services. But individuals in that age group have widely different developmental levels and under stresses of injury can return to more childish behavior patterns.

"While a 16-year-old trauma patient generally needs the same physical care as an adult with similar injuries, the kind of help required for more social needs — such as returning to school — can differ greatly between individuals. It's essential to understand each patient and how he or she is reacting to the situation," said Dr. Wharton, who also is an instructor in pediatrics at Harvard Medical School.

Team members also help hospital staff take into account how important such issues as appearance are to self-conscious adolescents. Ms. Gervasini recalled, "This summer a girl with beautiful long hair came in with a significant head injury. When she arrived here, she was conscious enough to plead with Emergency Department staff not to shave her hair.

"Instead of disregarding her wishes, they only shaved areas that were necessary for the operation and left the rest of her hair long enough to cover the bare spots."

Another situation seen in urban hospitals is children being injured in community violence. In those instances the MGH team focuses on preventing future injuries. "Some children don't even preceive the violent nature of their trauma as unusual," said team member Denise Lozowski, "which can make them particularly challenging to work with."

Dr. Wharton added that the loss of inhibition that can result from head injury makes prevention even more difficult. "Sometimes you have to meet with their friends and say, 'Listen, Johnny's not going to be able to control himself. You have to keep him out of situations where he might fight and get hurt again'."

Prevention is a major concern of all the team members. "We always look into what caused an injury and how it might have been avoided," Dr. Wharton said. "All of us are strong advocates for seat belts, bicycle helmets, community violence prevention programs, and other safety measures."

Dr. Wharton hopes that the work of the team — which, he said, currently is unique among Boston hospitals — will lead to educational programs for pediatricians participating in trauma care, an issue not touched on in his own education, he noted. MGH pediatric residents may be among the first to learn from the experiences of the Trauma Rehab Team.

He also credits several MGH staff members for essential support in setting up the team — especially Donald N. Medearis, MD, Chief of the Children's Service; Ronald G. Tompkins, MD, Chief of the Trauma Service; and Daniel P. Ryan, MD, pediatric surgeon.

"All of us who are involved with the care of children must be concerned with trauma," Dr. Wharton said. "It is the leading cause of death for children under 18 and results in 30,000 cases of permanent disability each year.

"Although it is not true that 'trauma is forever' — many kids do recover and return to their normal lives — we need to be able to follow these children closely for as long as they need our help." ■

# Chemical Key May Unlock Several Mysteries

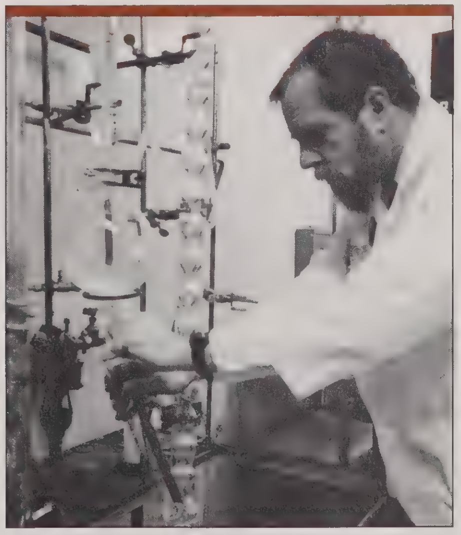
ONE IN FIVE Americans — about 62.7 million people — suffers from high blood pressure (hypertension). More than 90 percent of the time, the cause of the condition — which can lead to heart attack, stroke, or kidney damage — is unknown.

Now a team of scientists, led by an MGH researcher, has purified and determined the structure of a brain chemical that may play a key role in this so-called "essential" hypertension. Called hypothalamic inhibitory factor (HIF), the substance may be the missing link in the relation between salt intake and hypertension. It also could play a role in the treatment of some heart diseases.

HIF was originally isolated from brain tissue nearly 15 years ago by Garner T. Haupert, MD, and his colleagues (*MGH News*, December 1983). Produced in a part of the brain called the hypothalamus, which controls many of the body's automatic functions, HIF acts as a natural diuretic, stimulating the removal of fluids and salts from the body.

HIF produces its effect by slowing down the action of a molecule known as the sodium pump, found in each cell in the body. The sodium pump helps maintain each cell's proper chemical composition by pushing out ions (electrically charged molecules) of sodium and bringing in potassium ions. In cells of the kidney, which filters the bloodstream for impurities, the sodium pump plays a special role.

To maintain proper fluid levels in the body, more than 99 percent of the sodium filtered by the kidneys must be returned to the bloodstream by the sodium pump, instead of being excreted from the body in the urine. On the other hand, if too much sodium and fluid accumulates in the body — as can happen when people consume a lot of salt — the excess sodium must be removed. That is where HIF comes into play. The factor slows the kidney's sodium pumps and causes more sodium to pass into the urine, normalizing body levels.


*In the first step toward purifying an elusive brain factor, Dr. Garner Haupert used a 1930's-vintage flash distillation separator.*

But HIF can slow sodium pumps throughout the body, not just in the kidney. Dr. Haupert's group theorized that if HIF were released constantly — possibly in response to a kidney malfunction — muscle cells surrounding blood vessels would be affected. Slowing these pumps would also stimulate an accumulation of calcium ions inside the muscle cells, which would cause them to contract and raise blood pressure.

Therefore the tradeoff for returning sodium levels to normal would be the development of hypertension.

Proving this theory was difficult, however, because HIF is produced in infinitesimally small quantities. The factor had to be extracted directly from hypothalamus glands, which Dr. Haupert

*(Concluded on Page 8)*

## —A chemical key

*(Concluded from Page 7)*
acquired from the brains of beef cattle slaughtered in Midwestern packinghouses.

"For every ten pounds of this tissue, which represented more than 450 individual glands, we extracted about one microgram — that's one millionth of a gram [35 trillionths of an ounce] — of pure substance," said Dr. Haupert, who also is a physician in the MGH Renal Unit and an assistant professor of medicine at Harvard Medical School.

Completely separating such tiny portions from other factors in the tissue required development of a unique separation system (see box). Then — through the work of Dr. Haupert's chemist colleagues Adrienne Tymiak, PhD, of Bristol-Myers Squibb and Koji Nakanishi, PhD, of Columbia University — the exact chemical structure of HIF was determined.

With this knowledge, scientists now can artificially make sufficient quantities of HIF to investigate further its relation to hypertension. Under laboratory conditions, HIF does cause isolated blood vessels to tighten. But the factor's effects must be directly tested in living animals.

If the theory holds up — that HIF released to compensate for elevated levels of sodium and fluid in the body also causes blood vessel constriction — it could explain the association between diets high in salt (sodium chloride) and hypertension.

"We know that 50 percent of Americans with essential hypertension are salt-sensitive," Dr. Haupert said. "Their blood pressure rises when they ingest sodium, and cutting down on salt can improve their condition. HIF could definitely be the missing link between dietary sodium and hypertension."

Dr. Haupert believes that HIF will eventually prove to play a role in normal blood pressure regulation. Its effect on sodium pumps throughout the body implies a probable impact on other organ systems. With the group's discovery of HIF's structure, one intriguing possibility has already appeared.

Previously, scientists had observed that HIF produced effects similar to those of medications used to stimulate contraction of the heart — such as the drugs digitalis and ouabain. Dr. Haupert's group found that HIF's structure is quite similar to, but subtly different from, that of ouabain.

Plant-derived medications like ouabain and digitalis have been used for hundreds of years to treat heart failure, weakness of the heart muscle that prevents the organ from pumping enough blood. As important as these drugs are, they all have toxic side effects. These can range from nausea and visual distortions to arrhythmias — irregular heartbeats that can be life threatening.

Dr. Haupert believes the structural differences between HIF and the plant drugs could be responsible for the toxic effects. He notes that HIF applied to cultured rat heart cells does not produce the toxic effects seen with applications of ouabain.

"HIF is a natural, mammalian form of this type of compound, whereas ouabain and digitalis are plant-derived drugs. Animal tests of the synthetic version of HIF should show whether it has the effectiveness of the plant drugs without their toxicity." ■

## A Magnetic Solution

TO EXTRACT the miniscule amount of HIF present in a sample of hypothalamus tissue, Dr. Haupert's team devised a new strategy. The process used a powerful magnet, tiny magnetic particles, and sodium pump molecules isolated from animal tissue.

The magnetic particles were chemically attached to the sodium pumps, and the mixture was added to an extract of the hypothalamic tissue. There the pumps were attracted to and attached themselves to HIF. Application of the magnet to the container holding the mixture pulled the particle/pump/HIF complex to one side and held it there while the remaining material was removed.

A subsequent step under different chemical conditions released the sodium pumps with attached magnetic particles, leaving a pure solution of HIF. ■

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# Epilepsy Surgery Makes 'A Little Miracle'

WHEN THE ambulance braked at the doors of the MGH in the early-morning hours of March 13, the medical team on board sighed in relief. Throughout the night, as they raced back to Boston from northern Vermont, they knew that one of the biggest snowstorms in recent years was marching up the coast toward New England.

But while one storm had been beaten, another waited to challenge a team of MGH specialists. The patient who arrived in that ambulance was a five-month-old child whose brain was wracked by the electrical storms of severe, uncontrolled epilepsy.

Little Ian Pelkey appeared perfectly fine when he was born in October 1992. Although he seemed rather fussy at times and rarely slept through the night, generally he was an alert, happy baby.

But when he was about four months old, Ian began to "space out," recalled his mother, Lynn Pelkey. "At first we thought he was just starting to notice things, to focus on them. But then we realized it was more like he was going into a trance."

The episodes became more frequent and severe. The child's eyes rolled back in his head, his muscles became rigid — characteristic symptoms of epileptic seizures. By now Ian's parents knew that something was seriously wrong. On the advice of their pediatrician, they took the child to the Medical Center Hospital of Vermont in Burlington, 40 miles from their home in St. Albans.

The MCHV neurologists gave Ian a complete examination and prescribed standard anti-seizure drugs, which initially appeared effective. But the day after the child came home, the seizures returned.

Back in the hospital, Ian's condition

*(Continued on Page 4)*

*Now freed from almost constant epileptic seizures, Ian Pelkey is learning how to walk. The helmet protects his healing brain from the usual bumps and bruises of toddlerhood.*

## *Team Offers a New Option for Bladder Cancer Treatment*

FOR MANY years, patients diagnosed with invasive bladder cancer had no choice. Their only option for a cure was complete removal of the bladder and some surrounding structures — surgery that had a profoundly disruptive effect on their lives.

But now some patients are able to select a treatment strategy that preserves their bladder and appears to offer the same chance for curing their cancer. Largely developed through the work of physicians from the MGH Cancer Center, the treatment combines surgical removal of only the tumor with radiation and chemotherapy to remove any remaining cancer cells.

There are basically two types of tumors or growths found within the bladder. The most common begin in the organ's lining and grow into the inner cavity. These can be treated with drugs delivered directly into the bladder or removed via a cystoscope — a narrow tube passed into the bladder through the urethra, the passage that carries urine out of the body.

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## EDITORIAL

# A Quarter-Century Legacy

THE LAST 25 YEARS have seen unprecedented, some would say unbelievable changes in American medicine.

Procedures such as organ transplants have gone from being the stuff of front-page headlines to standard treatments. New imaging techniques — CT, PET, MRI — have given physicians views of the body that are startling in their clarity and detail, and PET and MRI have begun to unlock the secrets of the human brain. Advances in intensive care can save the lives of countless patients — from accident victims to premature infants — who otherwise would have died.

In the research laboratories of institutions such as the MGH, scientists have probed ever deeper into the cellular and molecular basis of human life and human disease. The gradual deciphering of the human genome — the genetic code that defines the individual biologic heritage of each human being — promises to open the door to curing genetic disorders.

Not all changes have been positive. While smallpox — one of history's great infectious scourges — has disappeared, it has been succeeded by AIDS, which has so far eluded the worldwide research community's best efforts to find a vaccine or a cure. Scientific advances have led to such bewildering ethical dilemmas as access to care, control of health-related information, and appropriate interventions at both the beginning and end of life.

Delivery of medical care has changed radically from what was almost entirely a one-on-one relationship between a patient and a doctor to one based on complex organizational structures like health maintenance organizations. Physicians and hospitals deal with ever-increasing levels of oversight from government agencies and insurance companies seeking to limit costs and define appropriate care.

The MGH has been assisted through the changes of this turbulent quarter-century by one constant presence. Martin S. Bander served as Deputy to the General Director and Director of News and Public Affairs from 1968 until his retirement last month. As the hospital's primary spokesperson, he explained a seemingly endless number of medical procedures and research discoveries to reporters and members of the general public. He advised three General Directors, members of the medical and research staffs, administrators and other employees on dealing with the news media. He shaped the development of this publication, and his opinions and impressions about issues from exercise fads to health care reform were expressed on this page.

There are those who cannot imagine the MGH without Martin Bander. His role was far greater than can be explained in a few words, and his influence will continue to be felt for years to come. Those of us who have been his colleagues can only hope to carry his legacy of wisdom, clarity, and integrity into the next 25 years. ■

## —Bladder cancer

*(Continued from Page 1)*

But about 30 percent of bladder tumors are invasive — that is, they have spread into the organ's muscular layer. These tumors — which have the potential to spread to other areas of the body — prove fatal in more than 50 percent of diagnosed patients.

Traditional treatment for these patients is a cystectomy – removal of the bladder and, for men, the prostate gland. Women undergoing the operation may also lose their uterus and part of the vagina.

After the operation, urine passes from the body through a stoma – a specially constructed opening in the lower abdomen to which a disposable collection bag is affixed. More recently, surgeons have begun constructing artificial bladders to collect urine inside the body. While some patients with artificial bladders can urinate normally, others must empty their bladders by inserting a small tube called a catheter into the urethra several times a day.

Because of both the impact on patients' quality of life and the unsatisfactory cure rate, cancer specialists have been looking for a better way. "The so-called gold standard of treatment for invasive bladder cancer just isn't good enough," said Donald S. Kaufman, MD, a medical oncologist at the MGH Cancer Center.

For years he and his colleagues have been investigating how chemotherapy and radiation therapy could improve

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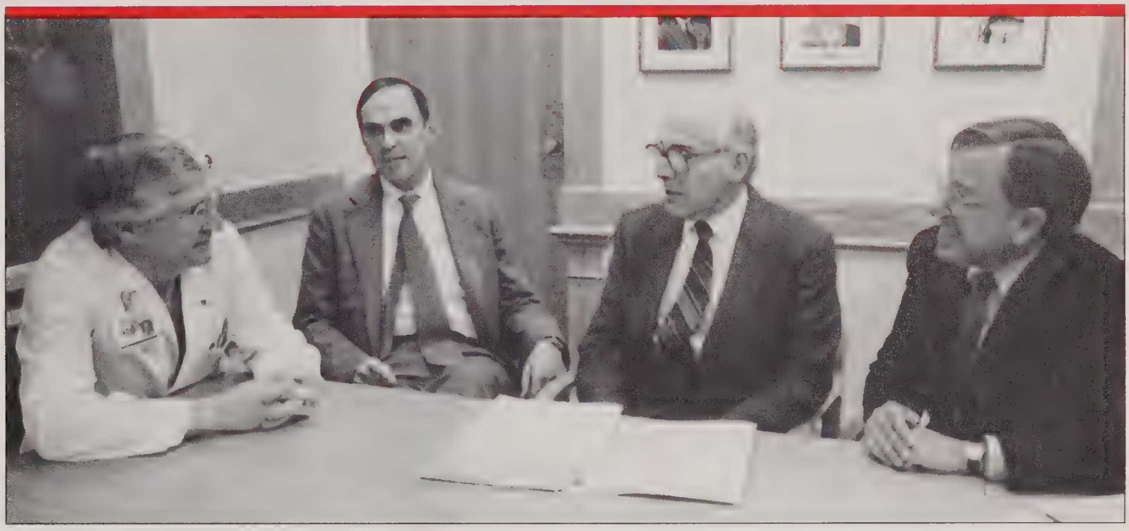
PHOTOGRAPHS: Page 1,5 courtesy of the Pelkey family; page 3,4,6,8, Susan McGreevey; page 5 image, courtesy of Dr. Andrew Cole; page 7 illustration, Arch MacInnes.

survival by destroying any cancer cells that might have spread beyond the area removed by the cystectomy. As advances were made in that area — including the introduction of newer, more effective drugs — urologic surgeons were also improving techniques to remove invasive tumors without perforating the bladder wall.

"We know that transurethral surgery [cystoscopic removal of just the tumor] alone can cure a few patients," said William U. Shipley, MD, an MGH radiation oncologist. "But we're unable to forecast who they will be. Similarly both radiation by itself and systemic chemotherapy alone can cure some patients. We've developed an effective combination of all three that is superior to earlier, single-modality approaches."

In a study recently published in the *New England Journal of Medicine*, Drs. Kaufman and Shipley — along with urologists Niall M. Heney, MD, and Alex F. Althausen, MD, and other colleagues — reported that their pilot study of combined treatment for invasive bladder cancer achieved a cure rate comparable to that of cystectomy. Of 53 patients participating in a program of tumor removal followed by chemotherapy and radiation, 24 (45 percent) were alive and free of detectable tumor after an average followup of 48 months.


*Members of the team working to improve options for bladder cancer patients: (from left) Drs. Niall Heney, Alex F. Althausen, Donald Kaufman, and William Shipley.*

Dr. Kaufman noted that this study's results — while encouraging — are only a beginning. The group is pursuing follow-up investigations that, they hope, may identify treatment refinements that improve the survival rate. And while bladder preservation is preferred, the overall goal always is to save the patient's life.

Two-thirds of the way through the course of chemotherapy and radiation treatment, the urologists check out the patients' progress. They do a cystoscopic examination — including a biopsy of the bladder wall — to see whether any cancer cells remain. If any tumor cells are found, the bladder is then removed. If the patient remains cancer-free, the final stages of radiation and chemotherapy are completed.

As with other forms of chemotherapy and radiation treatment, patients in this study did experience such side effects as nausea and low blood counts. The researchers are now investigating different types of chemotherapy to see whether these symptoms can be reduced.

One patient who participated in the program was Elliott Schneider of Sharon, Mass. Only 44 when he was diagnosed in 1988 (the average age of diagnosis is 65), he was referred to the MGH program after his health plan offered him only the option of total cystectomy.

"At the time I was treated, there were two protocols [programs of treatment] being tested — one with more chemotherapy and one with less. I was fortunate to have less chemotherapy, but even so I was intensely ill for a day after each treatment," he recalled.

"But it was worth it. Five years after my surgery I'm cancer-free and fully functional. I had spoken with some patients who had their bladders removed, and even with the artificial bladders they had to catheterize themselves and had no sexual function. The program may not work for everyone, but it worked for me."

While Dr. Kaufman expects that a large percentage of invasive bladder cancer patients might be candidates for this type of treatment, there are some for whom it would not be appropriate. These include patients whose tumor has caused enlargement of a ureter (the conduits that carry urine from the kidneys to the bladder) or those who could not tolerate the side effects of chemotherapy or radiation.

On the other hand, there are some patients whose medical condition would prevent them from undergoing the major surgery involved in a cystectomy. For them the combination treatment could be their only chance for a cure.

Both Drs. Kaufman and Shipley stress that this program has relied on close cooperation with the entire MGH urology group. "We've particularly benefitted from close cooperation with the urologic surgeons and other physicians in the MGH Cancer Center," Dr. Shipley said. "And the three nurse oncologists who work with us — Pamela Griffin in urology, Catherine Mannix in radiation oncology, and Camille Madden in medical oncology — have been invaluable to the program and to our patients."

The natural next step to evaluate a promising treatment like this one would be a large-scale, randomized controlled study in which equal numbers of patients are assigned to the newer and older forms of treatment. But Dr. Kaufman explains that this would be difficult since the overwhelming majority of patients want to try the organ-sparing strategy.

"There are many parallels between the way invasive bladder cancer has been traditionally treated and the way breast cancer was once treated, with disfiguring mastectomies," he said. "And just as many women who had the radical surgery used to die because their disease had spread, we still have too many patients who are not cured by radical surgery for bladder cancer."

"As we learn more about bladder cancer as a systemic disease [one that affects the entire body] and as we refine combination therapy with new drugs and better treatment plans, we hope eventually to be able to cure more patients while offering them a better quality of life." ■

# — Surgery creates 'a little miracle'

*(Continued from Page 1)*

became increasingly uncontrollable. Despite large doses of medication, he was soon having literally hundreds of seizures a day — sometimes without a stop.

"We knew we had to find a hospital better equipped to handle Ian's problem," Ms. Pelkey said. The Vermont doctors agreed and arranged Ian's transfer to the MGH.

Once Ian had safely arrived, the MGH specialists began a lengthy search for a cause of his seizures. Infantile epilepsy sometimes results from a brain injury occurring either before or during birth. In other instances, seizures are traced to abnormally developed brain tissue. Often no specific cause can be found.

Some seizures appear to involve the entire brain simultaneously, while others — called focal seizures — emanate from a specific area. The difference is important, as the generalized seizures respond better to medication.

The MGH team first conducted a 24-hour electroencephalogram (EEG). This measurement of the brain's electrical activity usually takes place over a couple of hours. But in cases like Ian's, specialists make readings over a full day with simultaneous video recording of physical activity. This allows neurologists to correlate overt symptoms with what actually happens in the brain.

Ian's readings showed the numerous, almost constant seizures, but the source of the problem was unclear. "At first it appeared that the seizures were very broad, rather diffuse throughout his brain," said MGH neurologist Daniel B. Hoch, MD.

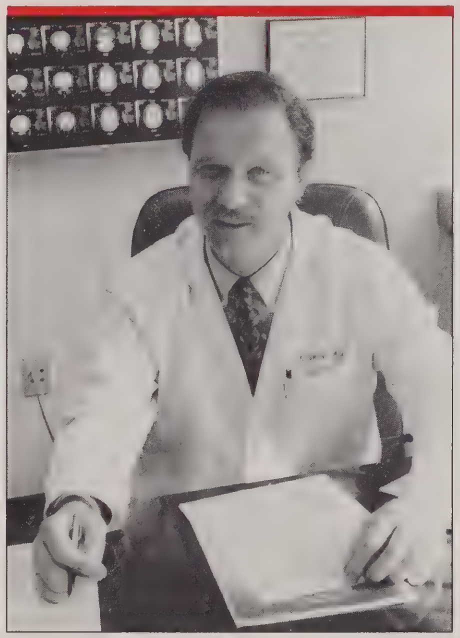
"But there also was evidence suggesting a focus of epileptic activity in the left frontal lobe [the part of the brain right above the eyes]. EEG readings taken in between seizures indicated a possible structural abnormality in the same area."

Following up this observation, the MGH team ordered a PET (positron emission tomography) scan, an advanced imaging technique — pioneered at the MGH and other institutions— that reveals activity within the brain.

"We were fortunate enough to get what's called an ictal PET — a PET image taken while he was in seizure — which clearly showed an area of overactivity in the left frontal lobe," MGH neurosurgeon G. Rees Cosgrove, MD, explained. "This led us to take another look at the MRI [magnetic resonance imaging] studies, which initially had appeared normal."

Close examination of the MRI, which gives a detailed look at the brain's structure, revealed a subtle area of abnormal tissue, also in the left frontal lobe. Additional MRI studies, specially processed to enhance the images, clearly identified the structural flaw.

The largest part of the brain, called the cerebrum, consists of a thin, outer layer of grey matter surrounding internal white matter. The grey matter contains the brain cells involved in thought, movement, and sensation; the white matter contains fibers that carry signals from one part of the brain to another.



*Dr. Rees Cosgrove*

Within the suspect portion of Ian's brain was an area of grey matter that was up to five times thicker than it should have been. This kind of abnormality — called cortical dysplasia — is known to be associated with epileptic seizures.

Identifying this structural flaw held out the possiblility that surgery to remove the tissue could relieve Ian's symptoms. But because the child was so young and because of the risks associated with any brain surgery, the MGH team first tried different medication-based strategies to control the seizures.

"You always exhaust the medical options before you go to surgery," said Elizabeth C. Dooling, MD, the MGH pediatric neurologist who oversaw Ian's care.

Initially the drugs reduced Ian's seizures to one or two per day — enough that he was able to return home for several months. But it was not long before the seizures again became more frequent.

"He just kept getting worse," Mrs. Pelkey recalled. "The doctors were trying different drugs, and he was in and out of the hospital up here. We really felt like we were grasping at straws."

One day before Ian was scheduled to return for a follow-up visit, he was again brought to the MGH by ambulance. "I knew he wouldn't leave without the surgery," his mother said.

"Of course my husband and I were scared to death," she added. "We knew that removing a portion of his brain had real risks — paralysis, loss of function — but we also knew that he wouldn't stand a chance if the surgery was not done."

In preparing to operate on Ian, Dr. Cosgrove and his colleagues turned to one of the most recent developments in imaging — computer technology that allows information from different kinds of images to be fused into a single picture.

A sophisticated MRI study provided a detailed three-dimensional image of Ian's brain that could be reproduced from any angle or cross-section. Then Hong-Jian Jiang, PhD, of the MGH Radiology Department combined that information with data on brain activity from the PET scan. (see sidebar)

"Fusing these two data sets gives you a representation of both the anatomy and function of the individual patient's brain. And we found that the area of over-activity from the PET scan correlated precisely with the anatomic abnormality from the MRI," Dr. Cosgrove said.

The picture created from the fused images also showed the pattern of folds and furrows on Ian's brain — a pattern that is slightly different for each individual. This information helped Dr. Cosgrove map the location of key areas controlling movement, areas to avoid in the operation.

"During the operation, we were able to recognize the features we'd seen in the images," he added. "What the computers were showing us was what we actually found during surgery."

Before removing the abnormal tissue, Dr. Cosgrove placed EEG electrodes directly on the surface of Ian's brain. Even though the child was under anesthesia with no evidence of seizures, the electrodes showed that cells in the abnormal area were firing in an epileptic pattern. The area was then carefully removed using standard neurosurgical techniques.

Since the operation in July, Ian has not had a single seizure and appears to be developing normally. Dr. Dooling noted that the child now wears a special helmet to protect his head as he is learning navigate the world as any toddler does. He also continues to take antiseizure medications. "After getting those seizures under control, we don't want to take any chances," she said.

Although the operation removed a significant portion of Ian's brain, his future prospects are quite good. "This was not normal brain tissue. It really did not have any function except to give rise to seizures," explained Dr. Cosgrove, who is also an assistant professor of neurosurgery at Harvard Medical School.

*Lynn Pelkey helps her son Ian celebrate his first birthday.*

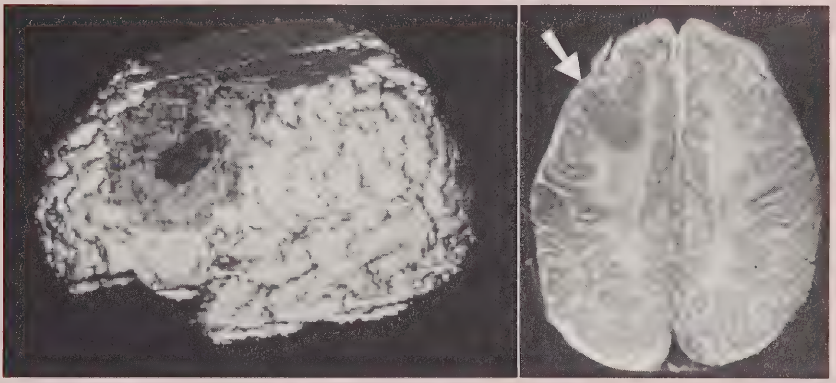
He added that in young children the brain is very adaptable. If an area controlling a particular function must be removed, that activity can be taken over by the corresponding area on the opposite side of the brain. "The younger the child is, the less likely there will be any deficit."

Andrew J. Cole, MD, chief of the MGH Epilepsy Service, pointed out that Ian's story shows how important it is to search for a potential structural cause of seizures.

"Right now we don't know how many cases of severe childhood epilepsy are associated with a structural abnormality, because doctors haven't always looked for one. In Ian's case, the standard MRI exam didn't allow us to diagnose him. We needed information from the more sophisticated techniques."

A few weeks after Ian's first birthday, his mother reported, "He's pulling himself up to his feet, trying to walk, and getting into everything. Sometimes I look at him and think, 'What a little miracle!' " ■

# *Images Create a Road Map for Surgery*



***Left:*** *This image of Ian Pelkey's brain combines information from both PET and MRI scans. The area of abnormal activity (darkest shading) appears in the center of the area of structural abnormality (medium shading).*

***Right:*** *This specially-enhanced MRI image shows the area of abnormally thick grey matter (arrow) in Ian Pelkey's brain.*

While none of the imaging techniques used to plan Ian Pelkey's surgery were unique to the MGH, his treatment represented one of the first combined uses of these methods in treating a patient.

The two types of imaging used — MRI and PET — both have advantages and disadvantages. MRI produces highly detailed images of the structure of bodily organs, but standard MRIs do not reflect how an organ is functioning. PET images show function but cannot pinpoint the activity's exact location.

Combining the great wealth of information produced by both methods required an intricate and powerful computer program, developed by Hong-Jian Jiang, PhD, a computer engineer in the MGH Radiology Department.

Bradley R. Buchbinder, MD, an MGH neuroradiologist, explained that most previous work integrating structural and functional brain imaging (some of which has been done at the MGH) focused on locating the sites of various activities — vision, hearing, thought — in the normal brain. Ian Pelkey's treatment may have been the first in which these techniques were used to create a map to guide an operation.

Neurosurgeon G. Rees Cosgrove, MD, said, "Most decisions about how you're going to do a procedure should be made before you enter the operating room. This kind of imaging helps the surgeon perform very detailed and individualized preoperative planning. When this gets integrated with other techniques we're using, we hope to be able to do smaller, more precise, and safer operations."

Dr. Buchbinder adds that the MGH researchers — including Drs. Cosgrove and Jiang and Nathaniel M. Alpert, PhD, of the PET lab — are also investigating the use of such integrated imaging in planning treatment of tumors, abnormal blood vessels, and other problems within the brain.

They also will be comparing the merits of PET to new MRI techniques that can show brain function (*MGH News*, October 1992). "If we could do all of this with MR, these techniques could have broader application, because only a few institutions are able to conduct PET scans. But we have to investigate that question scientifically." ■

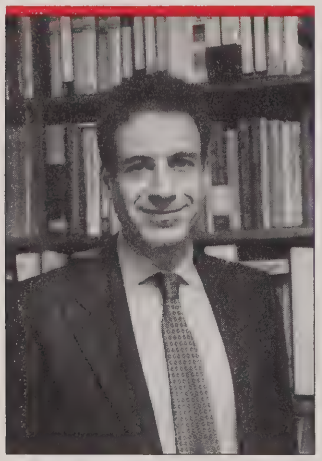
# A Way to Make Sense of Life's 'Deadly Choices'

What's a concerned person to do, when faced with a constant, often confusing barrage of health-related information?

One day a newspaper article appears touting the benefits of a low-cholesterol diet to prevent heart disease; the next someone publishes a book questioning whether diet has any effect on blood cholesterol levels. A story about the importance of maintaining a healthy weight is followed by a study showing that most people who lose weight regain it within a year.

Government panels, health advocacy groups, and research scientists issue recommendations and statistics about risks and precautions associated with everything from AIDS to exercise to cancer. But nowhere does the confused reader find the answer to the most important question: "What does all this mean to me?"

*"Our individuality is what determines what's important to us, and that gives us our freedom. Public messages can't focus on the individual. Each of us can make the right choice if we understand the information."*



*Dr. Jeffrey Harris*

One guide to finding that answer is *Deadly Choices: Coping with Health Risks in Everyday Life*, by Jeffrey E. Harris, MD, PhD, an MGH physician. In this recently published book, Dr. Harris directly addresses how each person must examine and interpret health-related information in light of his or her individual situation.

"I wrote this book because I have two lives," he explained. "In one life I am a research scientist who sits on government panels, makes recommendations about what the public should do, and talks with the media. In my other life, I see patients in my office who always ask me the same question: 'What does this mean to me?'"

Dr. Harris contends that each person's situation is unique and that individual situations must guide the choices that can make the difference between life and death. He chooses six areas to focus on: heterosexual transmission of HIV (the AIDS virus), exercise, weight control, cholesterol, cigarette smoking, and breast cancer. In each area he relates stories of people — based on composites of many patients — who face choices that could have a profound impact on their health.

A divorced woman decides whether to have sex with a man she is attracted to but does not know well. A man in his mid-40s must choose whether to continue in a rigorous aerobics class. An executive, worried about cholesterol, wonders how his luncheon menu will effect his chances of heart disease. A woman with a family history of breast cancer is urged to have a preventive double mastectomy by her sister, who has just been diagnosed with the disease.

None of these decisions are simple. For each, Dr. Harris reviews the latest information, explains arguments for and against particular choices, and shows how the people he describes might sift through all the data to find what works for them.

"My theme is that we *do* have choices," he said. "Our individuality is what determines what's important to us, and that gives us our freedom. Public messages can't focus on the individual. Each of us can make the right choice if we understand the information."

The task can seem daunting, he admits. One of his examples is a long-time smoker who — after at least nine unsuccessful attempts at quitting — feels another try would be useless. Placing the reader in the position of the physician, Dr. Harris outlines an extensive interview with the patient, during which he illustrates how "gentle, subtle scaring" could encourage this person to try quitting one more time.

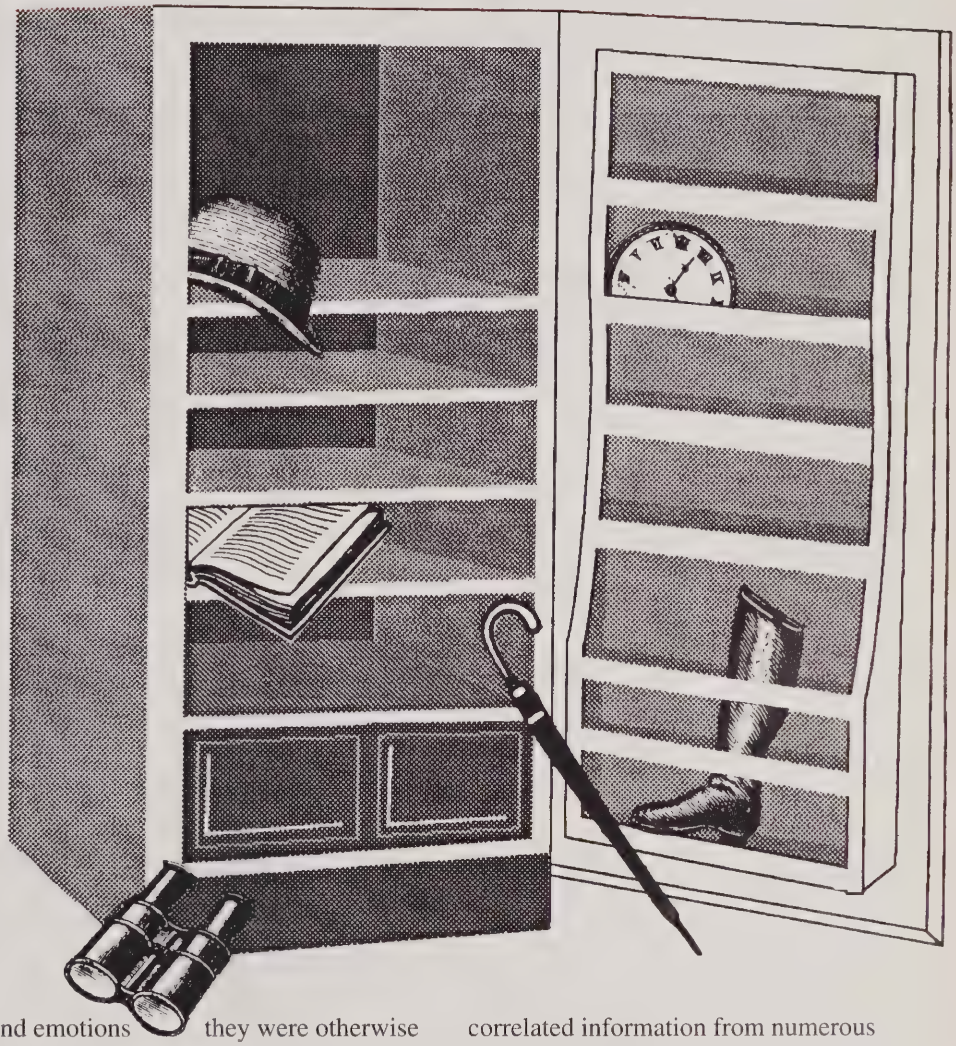
He then focuses on the primary problem associated with quitting: management of nicotine withdrawal. He describes how nicotine enters and affects the body when one smokes and outlines the usefulness and limitations of such aids as nicotine gum and the nicotine patch.

"This man feels like a slave to his cigarettes; he is convinced that he can't quit. But there are a lot of things out there — and more coming down the line — that could help him," said Dr. Harris, who is a professor in the Harvard Medical School/MIT division of Health Sciences and Technology.

"People see so much conflicting information that some of them just throw up their hands and do nothing," he added. "That kind of negativity certainly doesn't do any good. The right approach is not to hide from these issues but to confront them head on, to face the facts and sort out what makes sense for you." ■

# Exploring the Mysteries of Dreams

*We are such stuff as dreams are made of . . .*



DREAMING is as old as humanity — perhaps older — and people have wondered about the meaning of dreams throughout history. But until the last century, trying to understand dreams was largely the province of poets, priests, and prophets.

While Sigmund Freud was probably not the first to attempt a scientific investigation of dreams, his theories were the most comprehensive and became a starting-off point for subsequent psychological approaches to dreaming. Many popular ideas about the meaning of dreams spring from Freud's concepts — or from their misinterpretation.

Today, almost 100 years after Freud first published his theories, the understanding of dreaming continues to evolve. Knowledge of the physical basis of dreaming has led some to question the existence of any deeper, psychological meaning. Those who uphold the significance of dreams also recognize the limitations of Freud's ideas and are working to find better ways to understand what dreams can tell us about our inner lives.

Simply put, Freud's theory held that all dreams are representations of wishes or memories from infancy and early childhood. Because these thoughts were somehow forbidden, they always appeared in some distorted or hidden form in the dream.

"Freud had a theory that repressed infantile wishes or traumas generated aspects of adult behavior and were the motivation behind dreaming," explains Wynn Schwartz, PhD, of the MGH Department of Psychiatry. "In his model of the mind, these wishes were constantly seeking release, and the safest place for that release was during sleep."

Freud believed that these repressed thoughts were behind the neurotic symptoms of his patients and that uncovering and understanding such desires could lead to a cure. Discussing and interpreting patients' dreams became a key tool of psychoanalysis, the type of psychotherapy pioneered by Freud.

"Certain aspects of Freud's therapeutic approach have proven quite legitimate — getting people to talk and to feel and to become more comfortable with thoughts and emotions they were otherwise uncomfortable with. But his effort to connect the infantile wish with the adult dream was really based more on faith than on scientific data," Dr. Schwartz said.

Freud's insistence on a childhood origin for dreams always caused problems for psychoanalysts and other therapists, Dr. Schwartz added. "When patients tell us their dreams, we are rarely able to unravel them to a point of a childhood wish. What we hear instead, and what we have always worked with, is a kind of second opinion about how people organize their ongoing preoccupations, dilemmas, and opportunities."

That theory found support in a study conducted a few years ago by Dr. Schwartz and colleagues from the Boston Psychoanalytic Society and Institute — Ramon Greenberg, MD; Howard Katz, MD; and Chester Pearlman, MD. The group correlated information from numerous dreams reported by two study participants — a psychoanalytic patient and a student volunteer — with concerns and problems they discussed in meetings on the days before and after the reported dreams.

"We found that we could trace the majority of remembered content of the dream to what the person was thinking about during the day," Dr. Schwartz said. "And the way that content was worked on during the dream related to how the problem was experienced the next day — with a greater or lesser sense of mastery or sometimes with no change."

For example, in one session, the psychoanalytic patient reported struggling with his feelings about his father's death. Because he feared seeming weak, he wished to control the intensity of his sorrow.

*(Concluded on Page 8)*

## — Dreams

(Concluded from Page 7)

The following night he dreamt that he was held prisoner by two men who were forcing him to move his father's possessions out of a refrigerator. Although the dream began with a feeling of helplessness, as it continued he and his captors formed an assembly line that efficiently moved the items from one refrigerator into another.

The dream accomplishment gave him a sense of satisfaction, which the researchers interpreted as reflecting a successful effort to place his upsetting emotions into "cold storage."

"It appears that one of the functions of dreaming sleep is to master ongoing distress," Dr. Schwartz explained. "People seem more tolerant of their predicaments after a good night's sleep — specifically after a good night's dreaming."

This concept turns the Freudian view of dreaming upside down, said Dr. Schwartz. "Freud saw the content of the dream as essentially distorted, and it is true that the story lines of dreams are sometimes hard to understand. But my thinking is that dreams can be a way to undo self-deception, because what is seen often represents a person's sense of the world that is not as guarded, not as covered up by the face we wear when we meet other people."

While Dr. Schwartz and his colleagues continue to investigate ways in which dreams can be useful in psychotherapeutic situations, he notes that anyone can try to gain insight into their dreams.

"The first question you should ask yourself is 'Why am I having this dream now?' And then you should ask, 'How does this make me feel?' That's the beginning, and especially if you don't understand the dream, you might ask whether there's a theme that makes you uncomfortable and that you're avoiding recognizing," he said.

"If you can listen to your dreams — either by yourself or with some guidance — and develop a richer sense of yourself; if you can undo self-deception and get some clues about what's bothering you; if you can find richer ways of looking at the world than you may feel you are locked in to — that can only be helpful." ■

Dr. Wynn Schwartz

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# MGH/BWH Alliance Could Set Model for Future Health Care

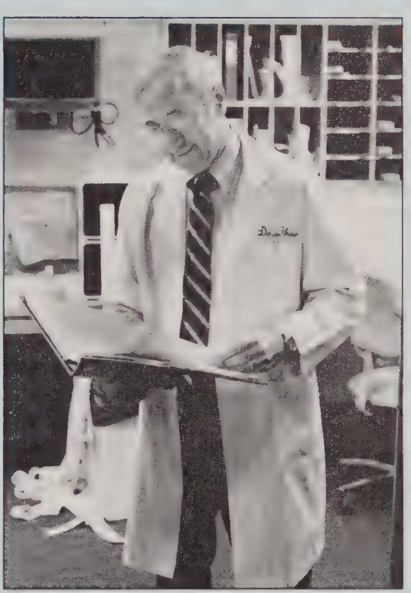
The decision of the MGH and the Brigham and Women's Hospital (BWH) to join forces positions the institutions as regional and national leaders in developing new approaches to health care delivery. The hospitals' combined efforts can now be directed toward building an efficient, smooth-running network that integrates primary care physicians, community health centers, and local hospitals with the best in tertiary care.

"Working together, two of the world's most prestigious medical institutions hope to create a model health care delivery system, focusing on delivery of top-quality patient care in the most cost-effective way," said J. Robert Buchanan, MD, MGH General Director.

The announced partnership represents the formation of a new parent company (temporarily named the MGH/Brigham Health Care System, Inc.) that will encompass the corporate structures of both the MGH and BWH, along with several affiliated corporations. Both hospitals will retain their individual names, identities, and facilities. And for the foreseeable future, all patient care services will continue to be delivered at the same locations.

*(Continued on Page 4)*

*MGH General Director Dr. J. Robert Buchanan (right) and Brigham and Women's President Dr. H. Richard Nesson (center) greet Boston Mayor Thomas Menino before news conference announcing the hospitals' partnership.*



*Samuel O. Thier, MD*

## *Dr. Thier welcomes the challenges ahead*

SAMUEL O. THIER, MD, looks on his recent appointment as president of The Massachusetts General Hospital as something of a homecoming.

"I'm very excited about this new opportunity. I've spent almost my whole life working in academic medicine and health policy. At a time when so many important issues are being debated locally and nationally, I'm delighted to return to medicine at the institution where I really got my start."

*(Continued on Page 2)*

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**Facing Breast Cancer Risks**
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EDITORIAL

# A Combination of Strengths

THE DECEMBER ANNOUNCEMENT that the MGH and the Brigham and Women's Hospital were going to join forces sparked surprise and speculation throughout the medical and news media communities. Predictions about the ultimate result ranged from the amusing — an editorial cartoon showing a patient being wheeled through rush hour traffic — to the outrageous — the assertion that one of the two institutions should cease offering inpatient services.

It is normal to wonder and worry how such a major step will affect each hospital's patients, employees, medical staffs, and local communities. It is also normal for members of the news media to construct scenarios of possible outcomes of such a momentous decision — that's part of their job. But it is also important to realize that much of what has appeared in the news media about the impact of the new partnership is speculation — speculation often colored by the particular interests, concerns, and opinions of the writer.

What is not speculation is that no health care institution can hope to get through the next few years without making major changes. No matter the eventual form taken by national health care reform, the effects of managed care are already being felt across the country. By combining their strengths, the MGH and the BWH hope to take a leading role in shaping new, more efficient ways of delivering patient care while maintaining their historic dedication to teaching and research.

The details of the MGH/BWH partnership will be worked out over many months. But one thing has been certain all along: both hospitals will maintain their individual identities and their dedication to meeting the needs of patients in their distinct communities. Meeting the combined goal of forming an efficient, integrated health care delivery system can only strengthen both hospitals and, ultimately, improve health care services for the entire region. ■

## —Dr. Thier

*(Continued from Page 1)*

The president of Brandeis University for the past two years, Dr. Thier has an outstanding career which includes six years as president of the Institute of Medicine of the National Academy of Sciences and 11 as chairman of the Department of Internal Medicine at Yale School of Medicine.

Dr. Thier received his internship and residency training at the MGH during the 1960s. He became chief medical resident and subsequently chief of the MGH Renal Unit before leaving Boston in 1969 to accept leadership positions at the University of Pennsylvania School of Medicine. Upon his 1991 return to the Boston area, Dr. Thier rejoined the MGH medical staff, participating in medical grand rounds and teaching rounds.

### *A redefined position*

The position of president of The Massachusetts General Hospital — the parent company that oversees seven affiliated companies — was redefined last year. Previously an unpaid volunteer, the president will now be a full-time chief executive officer of the parent company — which oversees the General Hospital Corporation ("the MGH"), McLean Hospital, Spaulding Rehabilitation Hospital, the MGH Institute of Health Professions, MGH Home Health Services, the MGH Health Services Corpora-

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PHOTOGRAPHS: Page 1 (left), 5, 8, Joshua Touster; Page 1 (right), 3, courtesy of Brandeis University; Page 6, Susan McGreevey. Page 6 diagram, Arch MacInnes.

tion, and the MGH Professional Services Corporation.

"My responsibility will be to provide overall leadership to the group," Dr. Thier explained. "We need to be sure we have a clear overall mission and a clear process for getting all of the affiliates to work together to streamline operations."

Dr. Thier also is expected to play a major role in negotiations leading to the planned partnership between the MGH and the Brigham and Women's hospital *(see Page 1 article).* He noted that this combination of two of the nation's leading teaching hospitals could lead to development of a model health care system for the next century.

"A lot of institutions are reacting to the changing environment by hunkering down and trying to change as little as possible," he said. "But that's not the right solution. The right solution is to move out in front of the changes and take an active role in redefining health care for this country. If first-rate institutions like the MGH and Brigham and Women's are not going to play a key role in that process, who will?"

As president of Brandeis, Dr. Thier was praised for the boldness of his vision, for the implementation of a new curriculum that is considered a national model, and for putting the university on a fast track to financial stability. While many of these changes were difficult, they were accomplished through a remarkable level of cooperation and enthusiasm throughout the faculty. Much of this success has been attributed to Dr. Thier's inclusive management style and his ability to identify problems and work cooperatively toward solutions.

### *Preparing for a time of change*

In his new position, Dr. Thier will be facing unprecedented changes in the country's health care system, changes that will have a profound impact on academic health centers like the MGH.

"American academic health centers are superb at providing technologically intensive, complex care — the best in the world. But they have not been economically efficient participants in the health care system. To fit in with the demand for cost-efficient care — along with the growing expectation for universal access to care — hospitals like the MGH will have to find new ways of doing business," Dr. Thier said.

He added that he envisions most academic health centers will eventually become part of larger health systems that provide a complete range of patient services — from primary care to the most complex, high-technology procedures — in a variety of settings. But such institutions will always play a unique role.

"Academic health centers are the only producers of new medical professionals and — along with a few specialized research institutes — the only producers of new medical knowledge. We have to hold on to those special missions while meeting new challenges."

Dr. Thier acknowledges that facing those challenges will not be easy, but he explained, "I like the viewpoint of the person who said, 'I am confronted with insurmountable opportunities.' We have some very exciting opportunities, and the fact that they are difficult and complex is all the more reason to try and solve them."

*During his years at Brandeis, Dr. Thier (center, right) has been known for his openness to faculty and student concerns.*

Realizing those opportunities will undoubtedly involve different approaches to delivering services, and it is generally accepted that hospitals in Boston and other major medical centers will be reducing their inpatient capacities. But Dr. Thier does not agree with those who predict a radical downsizing of the entire health care industry.

"It boggles my mind when people talk as though we're going to be cutting health care expenditures and services," he said. "What we're going to do — if we can — is constrain their growth and force some efficiencies on the system.

"The Boston area probably has more high-quality medical institutions per square foot than any other place in the world," he added. "As we try a variety of approaches to prepare for the future — mergers, affiliations, realignments of service — we don't want our success to imperil the future of any other hospital. The overall goals are better health care for our region and better models of health care for the rest of the country, not just to win an economic battle."

### *Strengths for the future*

Dr. Thier attributed much of the MGH's current strength to the leadership of J. Robert Buchanan, MD, who will retire as General Director this summer. He particularly acknowledged the hospital's physical expansion during Dr. Buchanan's tenure.

"He's basically redone this place, and took a bold move in establishing the Charlestown facility, which is a spectacular research center. He will be leaving an exciting institution with a premier group of people."

Dr. Thier continued, "This hospital has one of the greatest medical staffs in the world — both its world-class, full-time academic faculty and its extremely dedicated practicing physician group. I've never seen that combination as fully developed and committed as it is here. And the nursing and support staffs are just superb.

"Our affiliated hospitals — McLean and Spaulding — bring their own outstanding capabilities in the important fields of mental health and rehabilitation. And when you add the combined strength of the Brigham and Women's, the potential for the future is really spectacular." ■

# — MGH/BWH alliance could set model

*(Continued from page 1)*

### *Response to a new environment*

Although the decision to combine the hospitals seems sudden, it is a response to a phenomenon that has been growing more and more powerful for several years: managed care.

While managed care can take many forms, the basic concept is that a single primary-care physician — usually an internist, a family practitioner, or a pediatrician — coordinates all of a patient's care. The primary-care doctor determines when a patient is referred to specialists, who usually must belong to the same network of physicians, hospitals, and health professionals.

Health maintenance organizations (HMOs) are the most familiar type of managed care plan. The goals of such plans include reducing the amount of time patients spend in the hospital and reducing the amount of care provided by specialists. To keep costs low, programs negotiate with hospitals in the areas they serve to get reduced rates in exchange for including the hospitals in their networks.

The influence of managed care programs is being seen across the country. Although Massachusetts recently became the number one state nationally in HMO enrollment, with 35 percent of its population participating in such plans, the state has not yet felt the full impact of broad-based managed care.

In states where managed care is well established, the system's effects can be seen in greatly reduced numbers of patients admitted to hospitals and shorter hospital stays. Fewer patients in a hospital means that fewer beds are occupied and fewer inpatient services needed.

The money that hospitals receive for the patients they do admit is reduced both by concessions made to managed health care plans and by cutbacks in government reimbursement for Medicare and Medicaid patients. The coming national health care reform may shift virtually everyone to some sort of managed care system.

The growing emphasis on primary care also directs many patients away from specialty-oriented teaching hospitals and toward local community hospitals and physician practices. And, of course, a plan can decide to exclude a hospital from its network. For example, last year the Harvard Community Health Plan — the state's largest HMO — transferred most of its pediatric referral services from the MGH to the Children's Hospital.

One way the MGH has been coping with this challenging environment has been to build its own network of affiliations with local primary care physicians and community hospitals throughout Greater Boston *(see sidebar)*. While this process will continue, the new merger puts both hospitals in an ideal position to develop an integrated health system to serve the entire region.

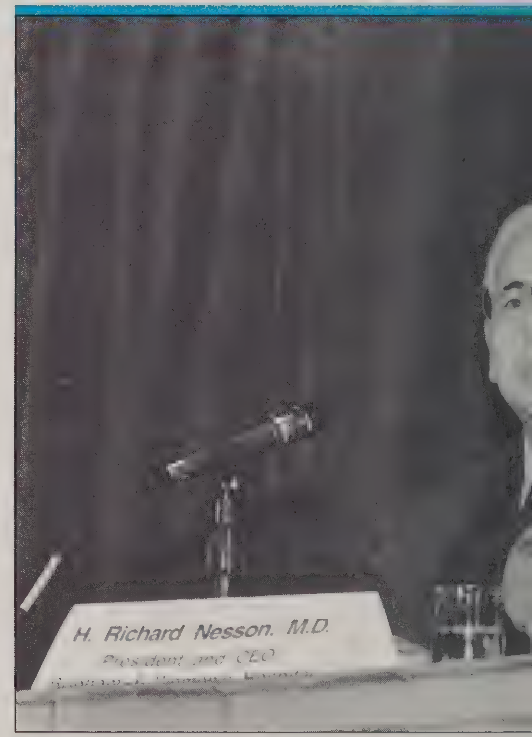
### *From competition to cooperation*

As the two largest Harvard teaching hospitals, the MGH and BWH traditionally looked on each other as rivals for patients, physicians, residents, researchers, and other employees. But an analysis prepared by the Boston Consulting Group revealed, at least in terms of patients, that perception was inaccurate.

In fact, the two hospitals tend to draw patients from different parts of the metropolitan area — the MGH from downtown Boston and the northern suburbs, BWH from Boston's neighborhoods and the western and southern suburbs. Combined statistics show that both institutions already provide a significant portion of the hospital care delivered in the entire

## Mission Statement

**Brigham and Women's Hospital and Massachusetts General Hospital are joining together in a commitment to better serve the needs of the community. Together, we are dedicated to taking a leadership role in an integrated, effective care delivery system and enhancing patient care, teaching, and research. We recognize that we can maintain excellence and leadership only by reducing costs of services and by attaining ever superior quality of care.**



Eastern Massachusetts region (except for the Cape and the Islands).

"This merger is an attempt to create the centerpiece of an expanded health care system — to use our combined resources to provide integrated and comprehensive care throughout the region," said James M. Richter, MD, an MGH internist and gastroenterologist.

W. Gerald Austen, MD, MGH Chief of Surgery, added, "This merger allows two superb institutions to join forces in an appropriate and sensible way. It's crucial that we don't stop here, that we keep developing our network of patient-care facilities."

### *First steps in a long journey*

The exact forms those cooperative efforts will take are yet to be determined. The process of completing the association has just begun, and it is sure to be a complicated one.

*Drs. H. Richard Nesson and J. Robert Buchanan at the December news conference.*

What *has* been accomplished is the appointment of a corporate board for the new parent company and a transition committee to oversee the merger process. This committee is forming task forces made up of administrators and physicians from both hospitals who will examine specific ways to improve operations, retain superior quality of care, and reduce costs.

While major changes are inevitable for both hospitals — and would have been even without this decision — some things will remain the same. The shared goals and philosophies of both institutions ensure continued strong commitments to top-notch patient care, cutting-edge research, and world-class teaching programs.

In many areas, the alliance will strengthen existing collaborations and pave the way for productive new partnerships. However, current research projects will be fundamentally unchanged, since most scientific grants are made to individual investigators.

Similarly, existing donor funds set up to benefit a particular hospital program or research effort will remain separate, and donors will always be able to specify an activity or institution they wish to support.

By being the first to take such a bold step to deal with the future of health care, the MGH and BWH may be able to help shape that future in ways that ensure the continued maintenance of their guiding principles.

"Our commitment to excellence has always stayed the same. But in the era of managed care and health care reform, the old approaches to fulfilling that commitment are no longer valid," said John Levinson, MD, PhD, an MGH cardiologist. "If all of us — physicians and administrators from both hospitals — work together to make this merger work, it will develop into something absolutely superb for the MGH and especially for our patients." ■

## Three New Agreements Enlarge Provider Network

Within the past few months, the MGH has announced the first of many anticipated agreements with community-based health care providers to form an MGH-anchored network. Affiliations are being formed with the Cape Ann Medical Center, a group of 11 internists based in Gloucester; the Massachusetts Associated Physicians, Inc., an association of over 170 physicians in the Framingham/Natick area; and The North Shore Medical Center in Salem.

The details of each agreement vary — ranging from partnerships with a primary care group and a developing physician/hospital organization to formation of a new 40-physician primary care practice. But at their core, each represents expansion of a network of community-based providers with ties to the MGH and features improved access for more patients to appropriate MGH services.

Richard von Reuden, MD, Deputy to the MGH General Director, said of these agreements, "The only way we can contain the long-term growth in health care costs is to work with a selective, committed network of providers and facilities to deliver integrated primary, secondary, and tertiary care in ways determined to provide high-quality results most conveniently and cost-effectively."

Several MGH physicians worked closely with administrative staff to craft agreements with community providers that uphold the shared goals of physician-directed care and patient advocacy. ■

# Scientists Probe Cell-Death Genes

A SCULPTOR working in clay molds a creation by both adding and removing layers of material until the desired shape appears. Similarly, human development involves not only the growth of cells and tissues but also the death of cells that are unnecessary, worn-out, or perhaps even dangerous.

Programmed cell death is the process by which certain cells die in response to their own genetic signals, instead of through some sort of injury. For example, the arms and legs of a developing fetus start out as undefined "buds." Cells multiply as the limbs lengthen, but the final formation of fingers and toes involves the death of cells in the webbing between each digit.

Countless incidents of the same sort of beneficial "cell suicide" occur during normal development and continue throughout life, keeping the normal renewal of the body's cells from getting out of control. But if the process goes wrong, the results can be devastating.

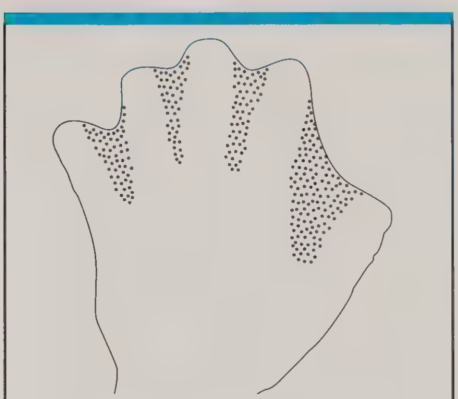
When cells continue beyond their normal life spans, one result can be cancer. Conversely, the death of brain cells seen in Alzheimer's, Parkinson's, and Huntington's diseases may result from inappropriate programmed cell death.

Recently a team of MGH researchers, working with colleagues from the Massachusetts Institute of Technology (MIT), identified what may be the first gene responsible for programmed cell death in mammals.

"The seeking of genes related to programmed cell death in higher vertebrates is a Holy Grail in this field. These are potentially major breakthrough findings," said Mark Fishman, MD, director of the MGH Cardiovascular Research Center (CVRC), to which the team of researchers belongs. Molecular geneticist Junying Yuan, PhD, is the team leader.

Dr. Yuan began investigating cell-death genes in the MIT laboratory of H. Robert Horvitz, PhD. Also on the MGH research staff, Dr. Horvitz led pioneering studies of cell death in the roundworm *C. elegans*. His team identified two cell-death genes in the worms, called *ced-3* and *ced-4*.

As a graduate student and postdoctoral research fellow in Dr. Horvitz's lab, Dr. Yuan and her colleague Shai Shaham (an MIT PhD candidate) were the first to clone *ced-3* and analyze the structure of the protein produced by the gene. They found the worm protein's structure was similar to that of a protein called ICE, which has been studied in both humans and mice. Because the similarities between the proteins occur in areas crucial to their activity, the scientists suggested that ICE could act as a cell-death gene in mammals.



*The development of a hand from an undefined embryonic "bud" involves both the growth of fingers and the loss of webbing (shaded area). The latter is an example of programmed cell death.*

ICE is known to act like a pair of scissors, snipping an important immune system substance — called Interleukin 1 beta (IL-1ß) — out of a larger protein. High levels of IL-1ß have been found in patients with Alzheimer's disease, head injury, and rheumatoid arthritis — all conditions that may involve programmed cell death.

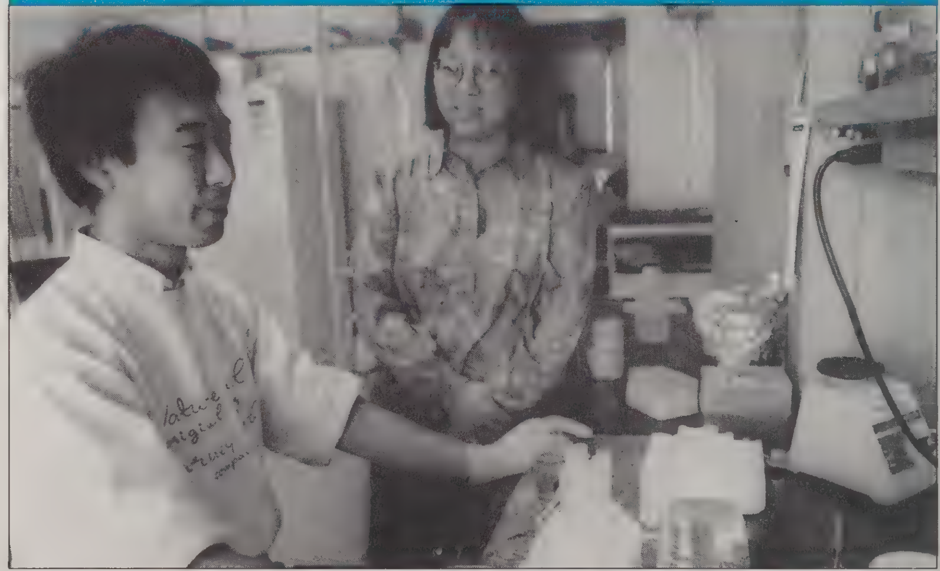
Dr. Yuan joined the CVRC research staff in 1991, and her team has been following up these discoveries. More recently, the scientists cloned the mouse version of the ICE gene and inserted the gene into cultured rat cells in a way that would lead to overproduction of the ICE protein. As expected, they found that the cells died in a process that looked like normal programmed cell death.

Even more significant, the team was able to stop the process of cell death by introducing a substance produced by the cowpox virus. The viral product was already known to inhibit the activity of ICE. In fact, it may be produced by the virus to defend against an immune-system directed programmed death of infected cells.

At this time Dr. Yuan and her colleagues think that ICE does not induce cell death through its processing of IL-1ß. Instead they believe that an unidentified protein, also clipped by ICE, is the trigger for programmed cell death.

The ability to halt the cell-death process could lead to new treatments for diseases involving excessive cell death — including Alzheimer's and Huntington's. If inappropriate activation of ICE is a factor in such illnesses, drugs that inhibit its activity — or that of other cell-death genes yet to be identified — could be be useful in treating or even preventing them.

"There's a lot more we need to learn," said Dr. Yuan, who also is an assistant professor of medicine at Harvard Medical School. "But someday these genes may be the basis of totally new types of therapies." ■



*Dr Junying Yuan (center) with Dr. Misayuki Miura, a member of her research team studying cell-death genes.*

# *Information, Support Help Women Face Breast Cancer Risk*

A NEW PROGRAM established within the MGH Comprehensive Breast Health Center offers information, reassurance, and access to the latest in care to women concerned about their risk of breast cancer. Through the Risk Assessment Program (RAP), a woman can receive an individual profile of her own personal risk level and recommendations for followup appropriate to her situation.

Increased media attention to breast cancer and activism among cancer patients and their supporters have produced greater awareness of the disease and much-needed increases in research funding. But the proliferation of information — not all of it accurate — has also brought confusion.

"A lot of women have an exaggerated viewpoint of what their risk truly is," said Deborah MacDonald, RN, MS, coordinator of the RAP. "We're here to help women understand what their risk factors really mean and — for those who are at higher risk — develop a plan for future screening, early detection, and support."

A visit to the RAP includes an examination by a surgeon specializing in breast disease followed by a meeting with Ms. MacDonald. This session allows a comprehensive review of the woman's individual and family medical history, discussion of her personal concerns, and a review of current knowledge about breast cancer risk factors.

"Many women have heard that the lifetime risk of developing breast cancer is 11 or 12 percent, and they think that is their own risk every day of their life. That is not true. " said Ms. MacDonald.

"Breast cancer is largely a disease of older women. For most women under 50, the risk is only 2 percent. It increases as they get older up to a total lifetime risk of 11 percent by age 85. But that figure is also an average of all women — some have a lower risk and some a higher risk."

Several factors are generally accepted as increasing a woman's risk of developing breast cancer *(see sidebar)*. Others — such as the role of fat in the diet, estrogen therapy, and environmental factors — are more controversial and are the subjects of current research.

It is important to note, however, that risk is only a measure of probability. There are high-risk women who never develop breast cancer and low-risk women who do. What risk assessment does is allow a woman to choose the combination and timing of screening techniques — regular breast self-examination, physician visits, and mammograms — that is right for her

Barbara L. Smith, MD, PhD, Director of the Comprehensive Breast Health Center, explained that follow-up care for most women seen at the RAP will be accomplished through their regular, primary-care physicians.

"We hope to provide a second-opinion service for primary-care physicians. We also hope that outside physicians will see us as a resource for evaluating patients whose risk may not be clear based on a standard examination. In addition, we are available to any patient who does develop a problem in the future who may choose to return to the Breast Center for specialty care," she added.

Women who are identified as being at higher risk through the RAP also will be given the opportunity to take advantage of new techniques being developed to detect and possibly even prevent breast cancer. These include an MGH Radiology study using two advanced imaging

*(Concluded on Page 8)*

## Breast Cancer Risk Factors

A WOMAN'S individual risk of developing breast cancer is based on the interaction of a variety of risk factors. Some of the most important factors are the following:

### Age

The single most important risk factor. The older a woman is, the greater her risk of breast cancer.

### Family History

Close relatives — particularly on the maternal side — who have developed breast cancer, especially at a young age, increase a woman's risk.

### Personal History

Women who have their first menstrual period before age 12, as well as those whose periods continue past age 55, are at increased risk. Also at increased risk are women who have their first child after age 30 and women who have no children. Recent studies have supported the observation that breast feeding may reduce cancer risk.

### Other cancers

Women who have had one breast cancer are at higher risk for a recurrence or development of a new cancer. In addition, certain other cancers — both in the woman and in her family members — can increase breast cancer risk.

Any woman concerned about her breast cancer risk is encouraged to call the Risk Assessment Program at (617) 726-9200.

## — Breast cancer

*(Concluded from Page 7)*

techniques — magnetic resonance imaging and positron emission tomography — to evaluate breast lesions.

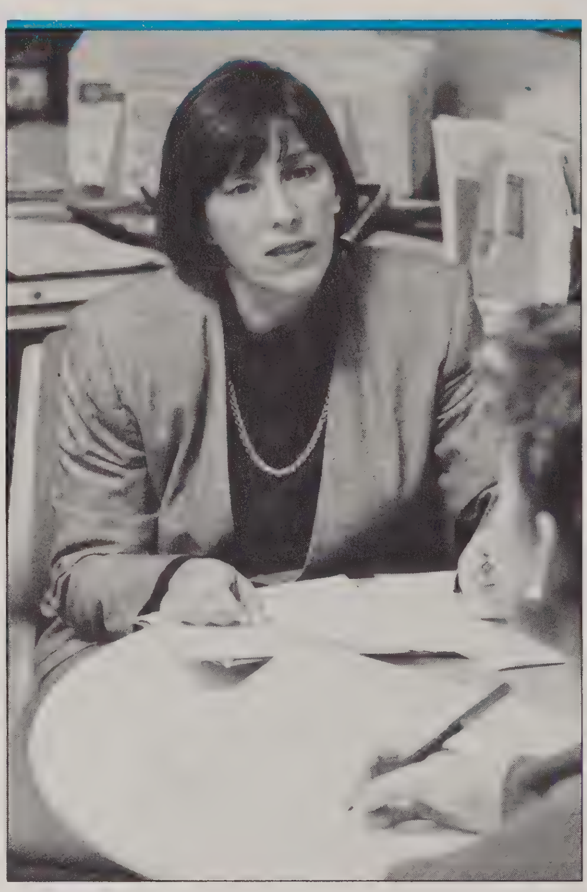
High-risk women meeting certain criteria are eligible to enter a national trial of the drug tamoxifen. Shown to reduce recurrence in women who have already had breast cancer, tamoxifen is being tested at the MGH and other centers to see whether it might keep cancer from developing in the first place.

Dr. Smith explained that this study marks a new era in breast cancer care — adding the possibility of cancer prevention to the steady progress that has been achieved in cancer treatment. Other positive signs include better understanding of how breast cancer develops and the probably imminent identification of a gene that causes a significant number of cancers.

> **"Early detection is a powerful tool that allows the great majority of patients to survive and live a normal life."**
>
> **Deborah MacDonald, RN, MS**
> **Coordinator, Risk Assessment Program**

That gene — called BRCA-1 (for breast cancer 1) — appears to be associated with the high incidence of both breast and ovarian cancer that appears in certain families. It also may play a role in non-inherited breast cancer if it is somehow mutated during a woman's lifetime.

The MGH has a special informational resource ready to be used when BRCA-1 or any other breast-cancer-associated gene is discovered and cloned. Molecular geneticist Stephen H. Friend, MD, PhD, has compiled a "library" of blood samples from 400 women diagnosed with breast cancer at age 40 or younger (*MGH News,* December 1992).



*Deborah MacDonald*

Once risk-associated genes are identified, researchers will be able to test the library's samples to see how often a particular gene is altered in women with cancer. That could reveal the relevance of a "breast cancer gene" in terms of the number of cancers it actually causes.

While discovery of cancer-associated genes holds out promise for better understanding of the disease, the information that is available today can be an important tool for women.

"I find that knowledge is power, both in treating women with breast cancer and in counseling those at risk," said Dr. Smith. "If you know the facts and what they mean for you and aren't just faced with some vague, frightening concept, you'll deal with your situation better, even when you have to hear bad news."

"Something that's essential to understand," added Ms. MacDonald, "is that no matter what your risk of developing breast cancer, your risk of dying from it is much, much less. Early detection is a powerful tool that allows the great majority of patients to survive and live a normal life. That's really the bottom line." ■

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# Operation Lets British Girl Breathe Easily

A unique operation devised by MGH thoracic surgeons has relieved a lifelong breathing problem — and possibly saved the life — of a young British girl. Twelve-year-old Rebecca Mitchell of Leicester, England, came to the hospital in January in search of a last-ditch solution to an unusual situation in which her body's major blood vessels literally threatened to strangle her.

When Rebecca was born, there were several abnormalities affecting the large vessels carrying blood away from her heart. The aorta — the body's largest artery — arises from the top of the heart and then curves downward, normally passing to the left of heart. Rebecca's aorta curved toward the right, a pathway that wrapped it around her trachea (windpipe) and produced a ring of blood vessels encircling the trachea. In addition, a major artery that branches off the aorta and carries blood to the arm was abnormally formed and positioned in a way that applied additional pressure to her airway *(see illustrations, page 5).*

Operations performed in her native England provided temporary relief, but as Rebecca grew, the constriction returned until it threatened to stop her breathing completely.

After a particularly dangerous episode in November, the British surgeons put a silicone tube in her trachea to hold it open. The solution was temporary at best and left Rebecca open to recurrent infections, including pneumonia.

The surgeons told Rebecca's parents that her best chance was with the MGH general thoracic surgery group, headed by Hermes Grillo, MD, an international leader in tracheal surgery. Within six weeks the local heart fund charity — of which the Mitchell family were longtime supporters — had raised the funds

*(Continued on Page 4)*

*Rebecca Mitchell (center) — shown here with her father Paul, mother Ella, and brother Spencer — a few weeks after the surgery that allowed her to breathe without obstruction.*

# *New Cardiac Chief is International Leader in Echocardiography*

Arthur E. Weyman, MD, newly appointed Chief of the MGH Cardiac Unit, assumes his new position with a sense of following in some historic footsteps. "It's an honor to follow in the path of people like Paul Dudley White, Edward Bland, and Edgar Haber," he said, referring to some of his predecessors.

The MGH Cardiac Unit has been instrumental in defining the specialty of cardiology since it was founded by Dr. White 82 years ago. And those chosen to lead the unit have always been among the most prominent in their field.

"Dr. Weyman is an international leader in cardiology who has made pioneering contributions in the field of echocardiography [the use of ultrasound to study the heart]," said John Potts, MD, chief of the

*(Continued on Page 2)*

## INSIDE

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**New Chief of Oral and Maxillofacial Surgery**
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## EDITORIAL

### *The Neighborhood, the Community, and the World*

WHEN A GROUP OF DOCTORS in England had exhausted all their options for treating a young girl whose abnormally-shaped blood vessels threatened to strangle her, they turned to the internationally-renowned thoracic surgery team at the MGH. Dr. Hermes Grillo — widely acknowledged as the "father of tracheal surgery" — and his colleague Dr. Cameron Wright used techniques from several different operations to relieve the pressure on Rebecca Mitchell's airway and give her a chance for a normal, active life.

Rebecca's story fits in with the image that many have of the care delivered at the MGH — a resource for highly technical patient care services, sometimes available nowhere else in the world. But that is only part of the story, because throughout its history the MGH has also been a community hospital, in the truest sense of the words.

MGH physicians deliver primary care to local patients in their offices or in the hospital's ambulatory care facilities, which had almost 600,000 patient visits last year. When in need, these Boston-area residents turn to the MGH as "their" hospital. In the communities of Charlestown, Chelsea and Revere, the MGH operates three neighborhood health centers that have nearly 200,000 patient visits annually. Each center is dedicated to providing complete primary care services for all community residents — from infants to the elderly.

In anticipation of national health care reform, and to deal with the ever-increasing shift toward managed care in Massachusetts, the MGH has been strengthening its primary care services, with a particular emphasis on community-based care.

We will always be proud of our reputation as an international center for specialty care, but that reputation rests on a strong foundation of service to patients in the region we call home. The expertise and dedication of MGH physicians, nurses, and other health care professionals is focused on meeting health needs of people from the neighborhood, the community, and the world. ■

## *—Dr. Weyman*

*(Continued from Page 1)*

MGH Department of Medicine. "I'm delighted that he will be leading our Cardiac Unit into the next century."

MGH Director of Cardiac Ultrasound since 1980, Dr. Weyman explained, "I was fortunate enough to begin my training at the time when two-dimensional cardiac ultrasound imaging was first developed. Today it is the most widely used imaging technology worldwide. If you're lucky enough to be in the right place at the right time, things can work out for you."

"Dr. Weyman took the initial two-dimensional technique and has used it to describe systematically all the structures of the heart," says MGH noninvasive cardiologist Robert Levine, MD. "He has shown that ultrasound is useful not only to make pictures of the heart but also to measure many aspects of cardiac function accurately, in order to produce the kind of quantitative information that is useful to clinicians."

### *Pictures Made from Sound*

Although most familiar for its use in examining unborn babies, ultrasound — the creation of images through high-frequency sound waves — has numerous medical applications. When used to examine the heart and related blood vessels, ultrasound can reveal structural details, information about how well the heart muscles function, and perhaps most uniquely

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PHOTOGRAPHS: Pages 1,5, Wendy Matarazzo; pages 3,4,7, Susan McGreevey; page 5 illustration, Arch MacInnes (based on drawings by Dr. Hermes Grillo); page 6 illustration, Arch MacInnes.

the speed and direction of blood flow.

The latter ability takes advantage of the Doppler effect, the alteration of sound that comes from an object as it moves past an observer. A common example of the Doppler effect is how the sound made by a speeding train seems to drop in pitch as it races past.

Doppler ultrasound is especially useful in examining patients with abnormalities in the valves that separate the chambers of the heart or control the passage of blood out of the heart. Problems with these valves can lead to turbulence in the flow of blood, as it leaks backwards through the valves. The motion-detecting ability of Doppler ultrasound gives a clearer picture of exactly how bloodflow is being disturbed by a valve defect.

"Our group has a longstanding interest in the structure and function of the mitral valve [the valve separating the two left-side chambers] and in the diagnosis of mitral valve prolapse [collapse]," Dr. Weyman said. "At one time it was thought that up to 20 percent of the population had this problem. Our work has narrowed that figure down to probably less than 1 percent that actually have the disease and need to be treated."

Other advances in cardiac ultrasound include transesophageal echocardiography — in which a sound probe is passed into a patient's esophagus, allowing studies to be done during cardiac surgery. The development of miniature ultrasound instruments that can be passed into the heart or coronary arteries during cardiac catheterization also offers new diagnostic possibilities.

### *Images from the Inside*

Readings taken from inside the heart allow echocardiologists to calculate the volumes of the heart's chambers and to more closely examine some of the organ's complex internal structures. Direct internal visualization of the coronary arteries is an essential tool in understanding the development of atherosclerotic plaques — fatty deposits that can eventually block the vessels and cause a heart attack.

Angiography (the other major blood-vessel-imaging technique) produces images reflecting the internal volume of a vessel, but it cannot reveal the presence of early atherosclerotic plaques that have not yet narrowed an artery's interior, Dr. Weyman explained. As researchers improve echocardiography's ability to depict the inner surface of a blood vessel, it will be possible to identify and study plaques before symptoms develop.

*Dr. Arthur Weyman (standing) reviews cardiac ultrasound images with Dr. Michael Picard.*

Dr. Weyman and his colleagues are currently researching the creation of three-dimensional echocardiographic images, including imaging the coronary arteries to evaluate the results of procedures designed to improve or restore blood flow. Through the use of powerful computer programs that analyze the ultrasound information, they are providing ever more detailed information on muscle function and blood flow within the heart.

### *A Changing Environment*

Discussing the challenges facing cardiology departments at teaching hospitals like the MGH, Dr. Weyman noted, "The whole clinical environment has changed. Obviously there are enormous external pressures to decrease the numbers of specialists and to make specialty programs more focused and efficient.

"But we will always need the kinds of tests and clinical services that can only be provided at the highest levels of university care," he added. "And as more and more care is rendered by primary care physicians, academic medical centers will need to expand their internal and external teaching mission."

In terms of patient-care and research challenges, Dr. Weyman cited several areas of interest that are currently being investigated at the MGH. "One major focus is the restenosis [renarrowing] of an artery that can occur after a procedure designed to open it up," he said.

"There has been an explosion of interventional technologies designed to deal with atherosclerosis, which have led to both some great successes and, in some areas, to failures and complications. One of our major goals is to try and optimize results of these therapies to provide maximum benefit for the patient."

Other MGH projects include investigating when a damaged heart muscle may be able to be "revived" after a heart attack and studying several aspects of heart transplantation, in collaboration with the Transplantation and Cardiac Surgery groups. The preventive cardiology program established in 1992 (*MGH News*, November 1992) continues to expand its search for ways to arrest the process of heart disease before symptoms occur and prevent future problems for patients who have already had heart trouble.

Dr. Weyman, who also is an associate professor of medicine at Harvard Medical School, is a fellow of the American College of Cardiology and past president and a member of the Board of Directors of the American Society of Echocardiography. He is the editor of the recently-published textbook *Principles and Practice of Echocardiography* and the author or co-author of numerous scientific papers, articles, and book chapters.

"As someone who trained with Dr. Weyman and has worked with him for over 10 years," Dr. Levine said, "I'd characterize him as a master teacher, researcher, and mentor. He's produced many leaders in cardiac ultrasound who are now chiefs of their own labs in this country and around the world." ■

# — Operation Helps British Girl Breathe Easier

*(Continued from Page 1)*

necessary to send Rebecca to Boston and to the MGH.

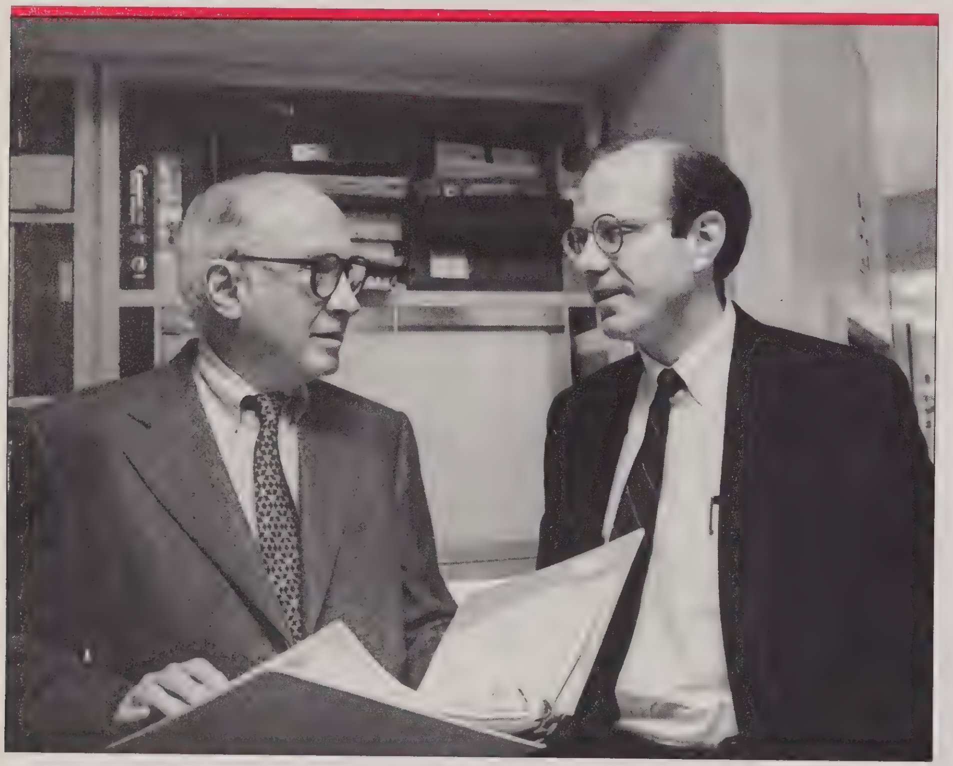
Throracic surgeon Cameron Wright, MD — a colleague of Dr. Grillo's — noted that while Rebecca's combination of problems was "exquisitely rare," the MGH team had actually seen a Dutch patient with the same set of abnormalities a few months before.

Dr. Grillo explained that the Dutch patient's doctors originally wanted the MGH surgeons to remove the portion of trachea that was being compressed, believing that the patient was continuing to have trouble after standard blood vessel surgery because that portion of the trachea had become soft. But on reviewing the patient's x-ray studies, Dr. Grillo became suspicious that an additional physical abnormality might be involved.

Closer examination confirmed that the patient also had an unusually shallow chest, making the space containing the heart, major blood vessels, and airway particularly confined. Instead of curving in a smooth arc, the aorta was forced into a tight, "hairpin turn," applying constant, throbbing pressure to both sides of the trachea.

So instead of operating on the trachea, Drs. Grillo and Wright concentrated on rerouting the blood vessels in such a way as to relieve pressure on the airway, which proved fairly successful in relieving the Dutch patient's symptoms.

When Rebecca's doctors described her situation to Dr. Grillo — and mentioned that they had already done the trachea surgery without a lot of success — he correctly surmised that the same sort of shallow chest was applying a particularly tight squeeze to her trachea and "hairpin" aorta.



*Drs. Hermes Grillo (left) and Cameron Wright*

The 12-hour operation performed by Drs. Grillo and Wright was similar — although not identical to — the one done on the Dutch patient. Slight differences in anatomy, as well as the changes made by previous surgeries, required an individual approach to Rebecca's situation *(see next page)*.

After the surgery, Rebecca received two weeks of specialized care in the hospital's Respiratory Intensive Care Unit, where staff members have particular expertise in managing postoperative care for thoracic surgery patients. By the time she was transferred to the thoracic/adolescent care floor, her condition had greatly improved; her airway had expanded to an almost normal size. In another week, she was ready to leave the hospital.

Dr. Wright explained that this operation — which he and Dr. Grillo have now performed on a third patient, a young American child — is an example of how surgeons can use techniques developed to deal with one type of problem to address another.

"In pediatric surgery it's not uncommon to reroute the blood supply to correct a congenital vascular defect. But I think this is a pretty unique way of repairing a tracheal constriction," he said. "With Dr. Grillo's expertise in this area — and he really is considered the father of tracheal surgery — we were able to apply those principles to help these patients."

Dr. Grillo added that the experience with Rebecca and the additional patients suggests that others with this set of blood-vessel abnormalities might be checked for the same sort of shallow chest that caused the hairpin-turn squeezing of the aorta. "If we could accurately diagnose these patients at the outset, we could treat them with a single operation, instead of putting them through several procedures."

Of course with such a new operation it is impossible to tell at this point what the long-term outcome will be. For now, Rebecca will be followed by her British thoracic surgeon, who will keep the MGH team apprised of her progress.

But for Rebecca and her family, the operation and the care she received at the MGH have made a huge difference.

At a surgical conference held right before her return to England, Rebecca told the audience that she felt, "really good. I'm much better than I could ever have imagined. I have to get used to it now."

"This has gone beyond our wildest dreams," said Rebecca's mother Ella. "We now can see a future for our daughter and our family." ■

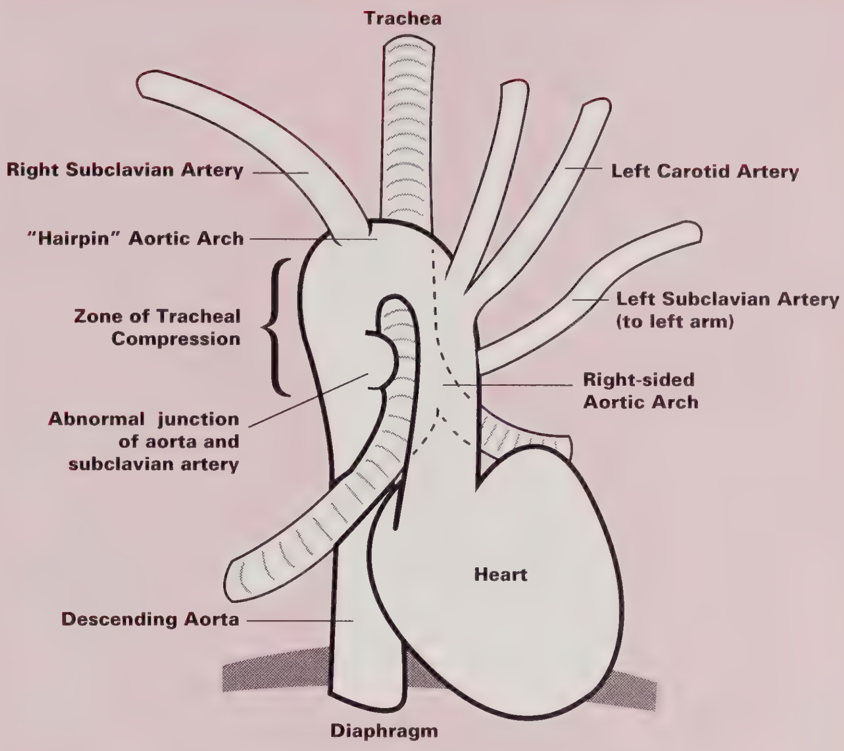
# Taking the Pressure Off

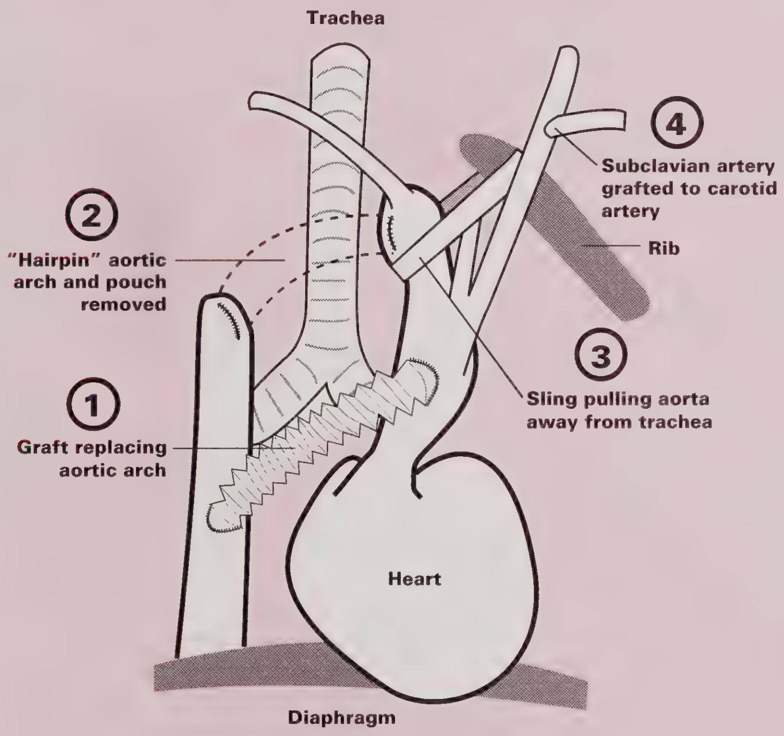
The complex operation that relieved the pressure on Rebecca Mitchell's trachea had four steps. *(see illustration, below right).*

First the surgeons attached an artificial graft to her aorta — running from just after the vessel left the heart to the descending aorta, which carries blood to the lower body — bypassing the "hairpin" aortic arch. Then they removed the compressed portion of the arch, including both the hairpin turn and the junction with the left subclavian artery (which carries blood to the left arm), where an abnormal pouching added additional pressure to Rebecca's airway.

With the new graft now carrying blood to Rebecca's lower body, the surgeons used a tiny sling (made of Gore-Tex) to pull the remaining portion of the upper aorta away from her trachea. Finally they attached the left subclavian artery to the left carotid artery, restoring the blood supply to her arm.

*Rebecca's high spirits are evident as she recovers from surgery.*


Trachea
Right Subclavian Artery
Left Carotid Artery
"Hairpin" Aortic Arch
Zone of Tracheal Compression
Left Subclavian Artery (to left arm)
Right-sided Aortic Arch
Abnormal junction of aorta and subclavian artery
Heart
Descending Aorta
Diaphragm


Trachea
4
Subclavian artery grafted to carotid artery
2
"Hairpin" aortic arch and pouch removed
Rib
3
Sling pulling aorta away from trachea
1
Graft replacing aortic arch
Heart
Diaphragm

*Above: The abnormal positioning of Rebecca Mitchell's major blood vessels put ever-increasing pressure on her trachea or airway.*

*Below: The complex, four-step operation rerouted her blood supply and released the strangling pressures.*

Note*: For purposes of clarity, several major blood vessels are omitted from these illustrations.*

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ARUBA
EGYPTIAN MUSEUM
10 L.E.
Melbourne
FIGUEROA
MARCOS
CUARTEL GENERAL DEL EJERCITO
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### Planning a Trip?

Advice on precautions to take against travel-related illnesses, vaccination services, and prescriptions for preventive medications all are available at the MGH Travelers Advice and Immunization Center.

To make an appointment, call (617) 726-3906.

# Center Helps Travelers Stay Healthy

THIS WINTER's endless snow and cold have sent thousands running to their travel agents with a single plea: "Get me out of here!" Travelers have been heading in droves for warm, sometimes exotic destinations in search of sunshine, relaxation, and adventure.

But unwary travelers may encounter something unexpected and unwanted in their exploration of tropical paradises — infections and illnesses that could ruin their vacation and even, in the worst case, threaten their lives. To decrease the chance that travelers will bring anything home with them but photos and souvenirs, the MGH Infectious Disease Unit offers a Travelers Advice and Immunization Center.

"We offer a comprehensive service to the international traveler, providing required and recommended immunizations, prescriptions to help prevent malaria and treat travelers diarrhea, and education to teach travelers how to stay healthy," said Donna Felsenstein, MD, head of the travel center.

Americans traveling in Canada, Western Europe, Australia, and Japan rarely encounter health threats different from those found at home. But in large areas of the world — including parts of Asia, Africa, and Central and South America — tourists need to take precautions against several major health problems. These can include malaria, typhoid, hepatitis A, polio, rabies, and yellow fever.

Dr. Felsenstein explains that there is only one illness for which vaccination is required to enter certain countries — yellow fever. However, wise travelers will also receive all recommended vaccines for the countries they wish to visit.

While there is currently no approved vaccine for malaria — one of the world's leading killer diseases — taking preventive medication can lessen the risk for travelers visiting areas where the disease is present. Use of insect repellents and sleeping under netting can also help avoid contracting this mosquito-born disease.

To avoid typhoid and hepatitis A, as well as the more common travelers diarrhea, travelers also should follow the well-worn advice — "Don't drink the water."

Dr. Felsenstein said, "We recommend that travelers drink only bottled water from sealed bottles — in some hotel rooms bottles have been refilled with water from the tap. Carbonated water is actually preferable, as that could not be replaced with tap water." Avoiding tap water also means no ice cubes, not swallowing water in the shower, and brushing teeth with bottled water, she added.

All food eaten should be cooked thoroughly, including fruits and vegetables, and salads should be avoided. It is best to choose fruits with a thickened peel that is removed before eating — like oranges or bananas — to insure the food is clean.

Water can also present another hazard: parasitic diseases that may be picked up by swimming in infected fresh water. Travel center staff can alert travelers to those areas where such illnesses — which include schistosomiasis — may be contracted.

A problem for which travelers may be unprepared is mountain sickness or altitude sickness, which can be encountered in this country as well as in mountainous regions around the world. Caused by the reduced oxygen and atmospheric pressure at altitudes greater than 8,000 to 10,000 feet, altitude sickness has symptoms that range from shortness of breath and headache to a potentially dangerous accumulation of fluid in the lungs and around the brain.

Precautions include making the ascent to high altitudes over several days and avoiding physical exertion until one is acclimated. Medications also can be prescribed to relieve the milder symptoms. But Dr. Felsenstein noted that altitude sickness and its more serious complications are particularly hazardous to people with existing heart and lung diseases, so much so that they probably should avoid traveling to high-altitude destinations.

"Actually anyone who has an underlying illness — such as diabetes, heart disease, lung disease, or depression of the immune system — should discuss any planned trip with a physician well ahead of time to make sure their itinerary is reasonable. The staff of the Travelers Advice and Immunization Center is specially trained to evaluate such situations and has the most up-to-date information about international health risks."

One final precaution that Dr. Felsenstein recommends is finding out where travelers can get medical help if they become ill — information that may be available through local consulates. "It's key to have a plan of action in advance," she said. "And it's also helpful to travel with a companion who can help you out if you become acutely ill while abroad." ■

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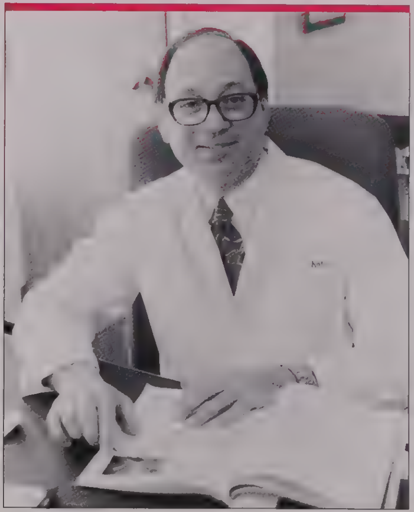
# *New MGH Chief to Lead Combined Harvard Oral and Maxillofacial Surgery Program*

THE APPOINTMENT of Leonard B. Kaban, DMD, MD, as MGH Chief of Oral and Maxillofacial Surgery is a homecoming of sorts for one of the field's international leaders. "My formative years were spent in Boston — at Harvard, at the MGH, and then at the Brigham and Women's (BWH) and Children's Hospitals. It's great to come back."

Dr. Kaban spent the last eight and a half years as chair of the Oral and Maxillofacial Surgery Department at the University of California at San Francisco. Among the inducements that lured him back to Boston was the opportunity to chair a newly-formed Combined Harvard Oral and Maxillofacial Surgery Program, which will encompass the MGH, BWH, and Children's programs.


*Dr. Leonard Kaban*

As leader of the MGH service, Dr. Kaban succeeds R. Bruce Donoff, DMD, MD, who is now Dean of the Harvard School of Dental Medicine. "Dr. Kaban was the best person identified in our search for a new MGH chief," said Dr. Donoff, who remains on the hospital's staff. "I'm very pleased that we were able to bring him back."

Dr. Donoff added, "The combined Harvard-wide program is a vision we've shared and been working toward for a long time. And it's truly consistent with the spirit of the new affiliation with BWH. Dr. Kaban will have my full support in his efforts to make the program a reality."

Although the three hospitals' oral surgery groups have collaborated for many years — with residents from the MGH rotating to the other hospitals — the combined program will formalize the relationship and allow both greater integration and flexibility of patient care, teaching, and research programs.

"Not only residents, but faculty members will be able to move between different hospitals, depending on their particular areas of expertise and interest," Dr. Kaban said. "We hope to have a bit more coordination of our clinical practices, to form a Harvard-hospitals oral and maxillofacial surgery group. And here at the MGH, I hope to streamline our operation to make it even more accessible to patients and referring physicians and dentists."

Dr. Kaban's patient care practice has focused on the problems of children — including treatment of growth defects affecting the face and jaw, facial injuries, and jaw tumors. His research interests are related — ways to induce the formation of new bone to repair a damaged area, and studies of wound healing in the fetus and how it may relate to treatment of inborn facial defects.

When surgeons reconstruct a portion of a patient's face or jaw that has been lost to injury or an illness like cancer, they currently must use bone taken from another part of the patient's body. The patient actually has two operations and endures additional discomfort and scarring. With colleagues in Boston and

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## — Dr. Kaban

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California, Dr. Kaban has investigated how bone material taken from deceased donors and subjected to a special treatment might be able to stimulate the growth of new bone tissue.

If a piece of bone is immersed in hydrochloric acid, the calcium and other minerals dissolve, leaving a framework made up of proteins, primarily collagen. It has been known for 100 years that if a piece of this framework — called demineralized bone matrix — is implanted beneath the skin of an animal, new bone will form in the area of the implant.

"The problem has been," Dr. Kaban explains, "that while we have always been able to use the demineralized bone matrix to form new bone in experimental animals, it has been very difficult to get it to work as well in humans."

Prospects for surmounting this problem have increased as scientists have discovered specific elements in the matrix responsible for bone formation. In recent years a whole group of these bone morphogenic (forming) proteins has been identified.

"We're hopeful that using these proteins will give us a more predictible, more exuberant response," Dr. Kaban said. "The direction we'll probably follow is to use bone-inducing matrix or proteins along with some sort of carrier material as an implant."

If successful, the bone formation research could not only make the repair of facial defects easier but also could improve the results of dental implants and be of use to orthopedic surgeons in speeding the integration of bone with the surfaces of artificial hips, knees, and similar implants. Dr. Kaban is working with Henry J. Mankin, MD, MGH Chief of Orthopaedics, and Julianne Glowacki, PhD, of BWH, to build a Harvard-based research team.

> ***If successful, the bone formation research could not only make the repair of facial defects easier but also could improve the results of dental implants and be of use to orthopedic surgeons.***

Dr. Kaban's wound-healing investigations take off from the observation that the healing process changes when an animal is born. A surgical incision made in a fetus heals without inflammation or scarring, two processes that can complicate the results of healing after birth. The challenge is to find ways to activate the fetal healing mechanism in the infant or adult animal.

One possible application of such research would be in the treatment of cleft lip and cleft palate — the most common congenital facial defect. While surgical repair of this condition is very successful, a significant portion of patients develop later growth problems affecting the middle of the face, problems that probably result from scar tissue.

In past studies, Dr. Kaban has shown that cleft lip repairs on fetal animals do indeed heal without scarring or subsequent growth defects. Now his former colleagues in California are searching for biochemical and other factors that may control the fetal healing process, and Dr. Kaban plans to start a similar effort at the MGH.

"It's important to note that no one doing this research is advocating surgery on human fetuses to repair cleft lip and palate," he stressed. "It's not appropriate to put the mother at risk to treat a non-fatal deformity that we can take care of after birth.

"But if we can find a way to make the postnatal healing process more fetal-like, we should be able to get better results for these patients and for others with congenital facial defects," he said.

Dr. Kaban also has been named the Walter C. Guralnick Professor of Oral and Maxillofacial Surgery at Harvard. Dr. Guralnick was MGH chief from 1967 to 1982 and continues on the hospital's oral surgery staff.

"The MGH is a great place, and it's exciting to be back at Harvard," Dr. Kaban said. "We really have a unique opportunity to build a center where practitioners from all over New England can send their oral surgery problems and patients can receive the very best care." ■

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# Making a difference for people with HIV

As scientific advances lead to longer lives for people infected with HIV, the virus that causes AIDS, patients and caregivers must deal with the disease's effects over several years and through many stages. And among the many ways the MGH helps people with HIV is through the services of the Robert B. Andrews Unit, established in 1988 to address the psychiatric and mental health needs of anyone affected by HIV.

The unit was named for Bob Andrews, a former MGH administrator who died of AIDS complications. Psychiatrist Jonathan L. Worth, MD, the unit's director, says: "Bob always supported putting patient care first. When we started this clinic, we thought he represented what the program was all about."

The unit now has a staff of 10 professionals — psychiatrists, psychologists, and a social worker — and offers a full range of evaluation, counseling, and support services to adolescents and adults with HIV, as well as their loved ones.

### *Help for the tough times*

Staff in the Andrews Unit handle a wide range of issues and problems. Many concerns are similar to those faced by any patient with chronic, terminal illness. Others are specific to AIDS.

"A lot of people with HIV/AIDS feel very isolated. There is still a stigma about the disease, and many of those infected belong to groups that are not widely

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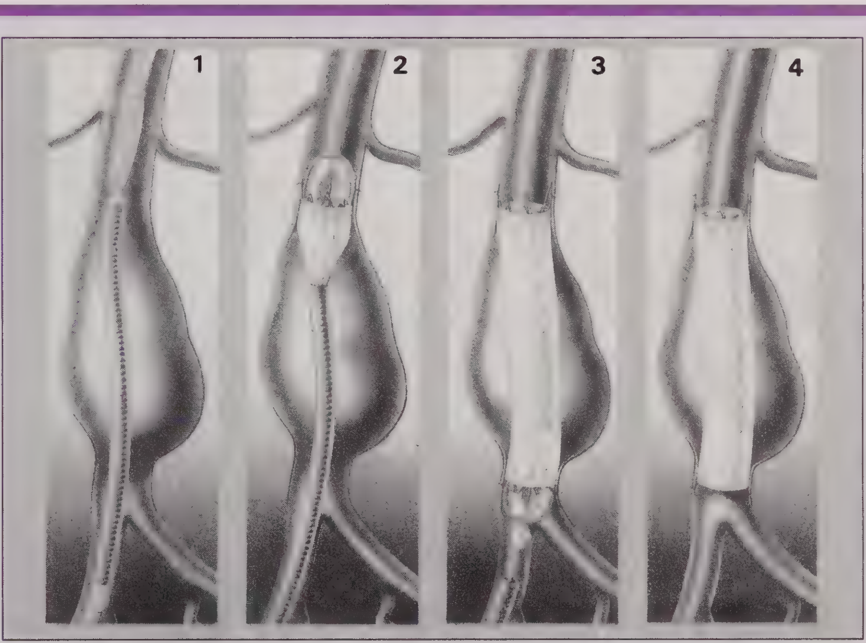

*1) Catheter containing custom-made graft and balloon apparatus is threaded into the aorta and through the aneurysm sac.*

*2) The outer capsule is slid back, releasing the upper attachment system above the aneurysm. Inflation of the balloon expands the system and secures hooks into the blood vessel wall.*

*3) The same technique is used to secure the graft below the aneurysm.*

*4) The catheter is removed, leaving the graft securely in place.*

# *Simplified aneurysm repair being tested at MGH*

A NEW TREATMENT option currently being tested at the MGH may greatly simplify the repair of abdominal aortic aneurysms. In some cases, the technique allows surgeons to repair dangerous swellings in the body's major blood vessel without the risks and inconvenience of major surgery.

An aneurysm is a balloon-like enlargement of a blood vessel, caused by a weakening in the vessel wall. As it grows and presses on adjacent structures, an aneurysm can cause a variety of symptoms or none at all, depending on its location.

But the most serious risk is that an aneurysm will burst. Ruptures of aneurysms in such crucial locations as the abdomen, chest, or brain (*MGH News*, June/August 1993) are life-threatening

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## EDITORIAL

# What's in a name?

IT'S OFFICIAL. The affiliation of the MGH with the Brigham and Women's Hospital is now called Partners HealthCare System, Inc. The new name was announced in March, upon completion of all legal requirements and final approval of the new system by both hospitals' governing boards and corporation members.

The name of the new system is more than just an exercise in "calculated neutrality," to adapt the words of one Boston reporter. The concept of partnership is, in fact, integral to the way the new system will develop. From the start, this affiliation has been one of two equal institutions, each having its own unique history and strengths while sharing a common dedication to outstanding patient care, teaching, and research.

Partnership will extend beyond the two major players in the new system. Both hospitals have relationships — some long-standing, some recent — with local and regional health care providers. Whether community hospitals, physician groups, neighborhood health centers, or specialty institutions like McLean and Spaulding hospitals, each of these will find its own level of partnership as the new system evolves. Additional institutions also may choose to join the system, further adding to the strengths that will be brought to meeting shared goals.

The system's embrace of partnership reflects a change that extends throughout this country's health care system. During the 1980s, experts promoted competition among hospitals and other providers as the way to hold down costs. Healthy competition will always have a role in spurring people and institutions to search for answers to scientific questions, develop more effective ways to treat illness, and find better methods to deliver excellent care at reasonable cost. But the health care realities of the 1990s have revealed the limits of competition, and forward-looking institutions like the MGH and BWH are turning toward collaboration to meet the new challenges of health care.

The process of building Partners HealthCare System has just begun. Ahead lie innumerable decisions that will affect each department, service, program, and individual involved. Sometimes greater integration of effort will be the solution, in other instances continued independence will be the best option. In the long run, success for the system as a whole will benefit each member of the partnership and, most important, will improve health services for the entire region. ■

## —Aneurysm repair

*(Continued from Page 1)*

emergencies.

Abdominal aortic aneurysms involve the major vessel carrying blood from the heart to the lower body. When these aneurysms rupture, the results are catastrophic. Less than half such patients even make it to the hospital, and less than half of those recover from emergency surgery.

The outlook is much brighter, however, when the aneurysm is detected before it causes any symptoms. Detection can occur in the course of a regular physical examination or when abdominal X rays or CT scans are taken for another purpose. Surgical repair of an abdominal aortic aneurysm is almost always the chosen course of action, unless the aneurysm is very small or the patient has other conditions that make surgery unusually risky.

While conventional aneurysm repair is usually very successful, it is a major operation. Any time surgeons must open up the abdomen, risks, including bleeding and infection, are involved. In addition, patients must spend about a week in the hospital, often with several days in intensive care, and full recovery can take four to six weeks.

The new technique, being tested at the MGH and a few other select centers around the country, utilizes techniques similar to those used to open up clogged arteries without surgery. A thin tube called a catheter is inserted through an

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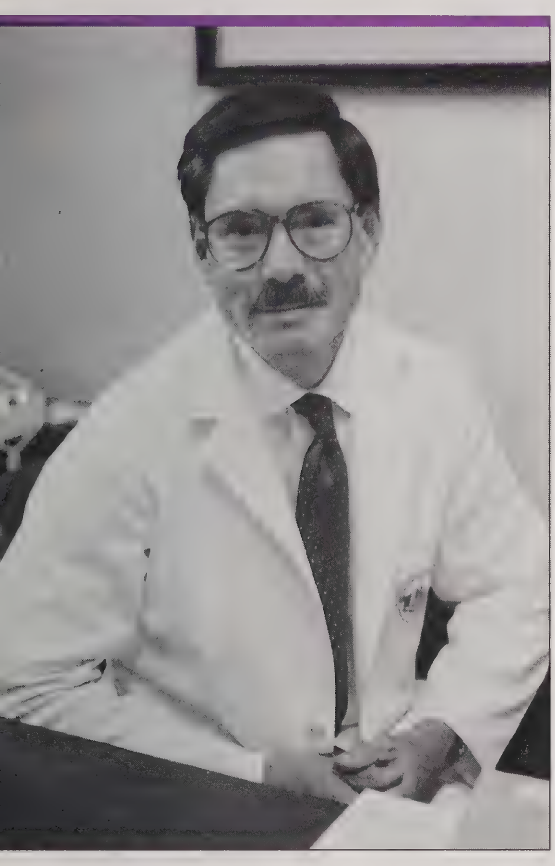
PHOTOGRAPHS: Page 1, diagrams courtesy of EndoVascular Technologies; pages 3,4,5, Susan McGreevey; page 6, Wendy Matarazzo.

artery in the leg (the femoral artery) and threaded up to the location of the aneurysm.

Under the guidance of fluoroscopy (continuous x-ray images), the surgeon inserts a polyester graft (an artificial blood vessel), which has been tightly rolled up within a capsule at the end of the catheter. The ends of the graft are secured above and below the aneurysm with metal hooks and pressed into place by inflating a tiny balloon *(see Page 1 illustration and sidebar).*

"Repairing an aneurysm through a catheter is a much, much less extensive procedure that should take significantly less operating time," says David C. Brewster, MD, the MGH vascular surgeon who is testing the technique. "But the most striking difference is the postoperative recovery."



*Dr. David Brewster*

The first patient who participated in Dr. Brewster's trial, Yefim Frid of Brighton, was able to go home the second day after the procedure. Mr. Frid, who was 83 at the time of the surgery last year, was actually in the hospital waiting for the conventional operation when a diagnostic study showed his aneurysm was ideal for the graft technique.

"Dr. Brewster called me the evening before the operation was scheduled and said they could do another kind of surgery that was much easier and much less risky," said Mr. Frid's daughter Irene Simon. "We were surprised and very glad that he had this opportunity. Today, my father is just fine."

The graft system, developed by EndoVascular Technologies of California, has already been tested in what is called a Phase 1 trial, a limited study focusing on whether the procedure is safe. The current nationwide investigation is a Phase 2 trial, designed to compare the treatment to standard surgical repair.

Investigators at 13 centers — the MGH is the only one in New England — hope to enroll 150 patients. Half will receive conventional treatment and half the new procedure. If results are as good as expected, the new graft will be approved by the US Food and Drug Administration for general use. Dr. Brewster is the principal investigator at the MGH, and William M. Abbott, MD, and Richard P. Cambria, MD, both vascular sugeons, are co-investigators.

"In addition to comparing how well the two techniques repair the aneurysm, we will evaluate both improvements in recovery time and any cost benefits," Dr. Brewster says. "And of course we'll keep a close watch out for any unforeseen problems with this technique, especially whether it holds up as well as the standard graft."

Dr. Brewster says that the graft currently being tested is appropriate for only a small number of abdominal aortic aneurysms, those that occur below the arteries supplying the kidneys and above the place where the aorta branches into two smaller arteries leading to the legs. The developer, however, is currently working on a bifurcated (Y-shaped) graft that could be used to treat more extensive aneurysms.

If the new technique proves successful, it also could be used to treat other blood vessel defects — such as an abnormal connection between an artery and vein. In addition, some patients with medical problems that make surgical aneurysm repair too risky might be able to undergo the less invasive new procedure. (Most such aneurysms occur in people over 60.)

"I believe that this procedure is going to be an important advance that eventually will replace standard surgical aneurysm repair in many cases," Dr. Brewster says. "It's an exciting opportunity that should allow us to improve patient care while further reducing costs." ■

## *New graft offers a custom fit*

Conventional repair of abdominal aortic aneurysms requires surgeons to open up the abdomen and move aside internal organs to expose the aneurysm site. Then they open up the aneurysm, remove any debris inside, stitch in a graft connecting the normal vessel above and below the weakened sections, and reclose the aneurysm around the inserted graft.

In the new endovascular (within the blood vessel) technique, a catheter is inserted through a small incision in the groin and passed into the aorta through the femoral artery. At the end of the catheter is a capsule containing a folded-up graft — an artificial blood vessel made from a special impermeable polyester, which must be custom made to fit the patient's aorta. At each end of the graft is a collapsible metal attachment system.

Once the catheter and graft are in place, the outer capsule is gradually retracted. As the upper portion of the folded-up graft is released, the upper attachment system springs open *(see Page 1 illustrations).* A balloon is inflated inside the system to anchor the tiny metal hooks into the blood vessel wall. Further retraction of the capsule releases the rest of the graft, and the balloon is used to fully open and anchor the lower attachment system.

The catheter and balloon are then removed, leaving the graft securely in place. ■

*(Continued from Page 1)*
accepted in our society," Dr. Worth says.

"But most people with HIV/AIDS don't need long-term psychotherapy," he adds. "Instead they need short-term help in dealing with particular events — when they first get diagnosed, when they first have symptoms, when a friend or loved one dies. Whenever they hit these tough times, they come back to us."

One area being studied by Andrews Unit staff members is the effect of HIV infection on the brain and nervous system. MGH researchers Bradford A. Navia, MD (then at Cornell), and Martin S. Hirsch, MD, with David Ho, MD (now at UCLA), were independently among the first to confirm that the virus directly invades nerve tissue, producing symptoms ranging from pain in the extremities (neuropathy) to a loss of certain mental abilities (dementia) and changes in behavior.

> ***"Most people with HIV/AIDS don't need long-term psychotherapy. Instead they need short-term help in dealing with particular events — when they first get diagnosed, when they first have symptoms, when a friend or loved one dies. Whenever they hit these tough times, they come back to us."*** ***— Jonathan L. Worth, MD***

HIV infection can cause these neurological problems in several ways. Immune system suppression may lead to opportunistic infections or tumors in the brain itself. In addition, changes in hormonal levels related to effects on other organs can indirectly produce neurologic symptoms or changes in thinking processes. Medication side effects also can affect the nervous system.

But the most insidious and probably most feared effects are those of HIV brain infection — the changes in thinking and emotional processes called HIV dementia. The mechanisms of dementia are unclear. The virus itself may damage brain cells directly, or substances released by the immune system, in an effort to fight infection, may have their own toxic effects.

Symptoms of HIV dementia include loss of attention span or ability to concentrate, trouble with short-term memory, and difficulty keeping the thread of a conversation or finding the right words. In the early stages, such symptoms can be subtle and hard to distinguish from the mental lapses that anyone can experience, especially when under stress.

### *Computer-based tests aid diagnosis*

As a first step in diagnosing patients with HIV dementia, Andrews Unit staff members use a group of simple, computer-based screening tests.

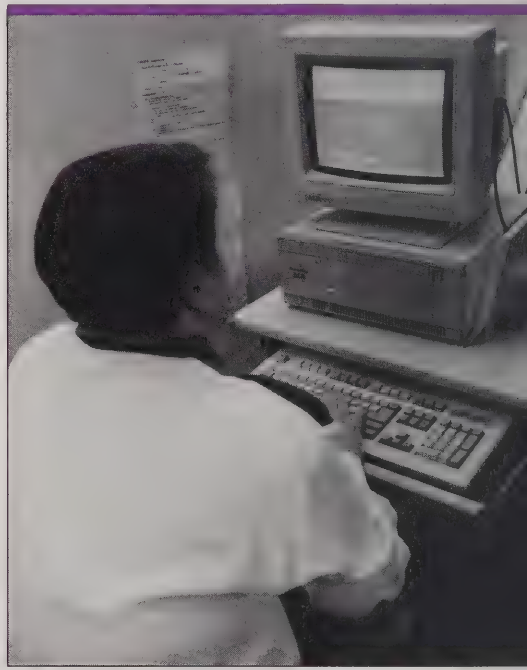
Dr. Worth explains: "In these screening tests patients sit alone at a computer and work through a five-minute series of tests. They can take their time and are not intimidated by anyone watching them take the tests."

Originally developed at UCLA, the tests were refined at MGH for HIV dementia by Cary Savage, PhD, a neuropsychologist, and Dr. Navia, who is a neurologist. Trials with both patients known to have HIV dementia and an HIV-negative control group proved the tests were effective in detecting HIV dementia.

The tests measure reaction time in increasingly complex situations. "In the most sensitive test, a sequence of two numbers appears on the computer screen, and the person is instructed to respond only when a number is followed by the next larger number, say a 7 followed by an 8," Dr. Savage explains.

"That taps into what is called 'executive function,' which includes the ability to keep several instructions in mind, respond quickly and accurately to the appropriate signal, and suppress an inappropriate response. That's just the sort of thing patients tell us gives them trouble."

Dr. Savage adds that taking the test can be reassuring for HIV-infected people who do not prove to have any measurable changes. "Many of them are very worried. They've read about HIV dementia, or AIDS dementia complex, and wonder if they have it too. And this lets us know that any cognitive [thought-related] symptoms they have could be related to stress or another problem that we can treat very effectively."



*By measuring reaction time, a simple, computer-based test can help identify patients with HIV dementia.*

While treatment options for those with dementia are limited, drugs like AZT that fight the virus can help slow the progression of symptoms.

"Things are a lot different than they were before AZT," Dr. Worth says. "We used to see a lot of people with very severe dementia who progressed very rapidly. AZT may not improve function over the long term, but it seems to slow progression of dementia or preserve function for a while."

### *New drugs hold promise*

Some newer antiviral drugs or drug combinations being tested at the MGH and elsewhere may prove even more effective in slowing dementia. And other drugs that target the virus's action in the brain are also being tried. If such medications prove effective, early treatment of dementia could make a significant difference in patients' quality of life.

One drug of interest is nimodipine, which may block the toxic effects of a part of the virus called gp-120. A preliminary trial of the drug's safety — led by Dr. Navia and Stuart Lipton, MD, of Children's Hospital — has just been completed by the AIDS Clinical Trials Unit. A larger study to compare the effectiveness of nimodipine to other types of therapy will start this summer.

This trial is part of a major research grant to establish a national consortium of centers, based at the MGH, to study neurologic aspects of AIDS. Dr. Navia is the program's principal investigator. Other studies funded through the grant include trials of a drug to treat PML (progressive multifocal leukoencephalopathy), a disease affecting the white matter of the brain, and trials of antiviral drug combinations for advanced neurologic disease.

### *Links to depression*

Another question being pursued by Andrews Unit investigators is how the physical changes caused by HIV in the brain are linked to depression. Studies have included the use of magnetic resonance (MR) spectroscopy to look for changes in the brain's chemical activity and some of the latest imaging techniques to examine alterations in blood flow. Along with Drs. Worth and Navia, collaborators in the brain imaging work include R. Gilberto Gonzalez, MD, PhD, in the MGH Imaging Center; B. Leonard Holman, MD, and Keith A. Johnson, MD, at Brigham and Women's Hospital; and Perry F. Renshaw, MD, PhD, at McLean Hospital.

"Some patients may become depressed not as a reaction to their situation but because of HIV's effects on areas of the brain responsible for emotion," Dr. Worth says. "If antidepressants worked against HIV, it wouldn't matter what the specific cause was. But if there is underlying HIV disease in the brain, you might want to try AZT or another antiviral drug first."

### *Assessing quality of life*

All of the work of the Andrews Unit — from counseling to drug trials — aims to improve the lives of people with AIDS. But when there are still no therapies available that cure the disease or reverse the symptoms, both patients and caregivers may wonder whether treatment can achieve any real difference, especially when available drugs like AZT can have serious side effects.

MGH psychologist William Lenderking, PhD, and colleagues at the Harvard School of Public Health have been developing tools to evaluate the quality of life of people with AIDS. Dr. Lenderking's group examines such issues as patients' perceptions of their physical and emotional well-being and the importance of physician-patient communication.

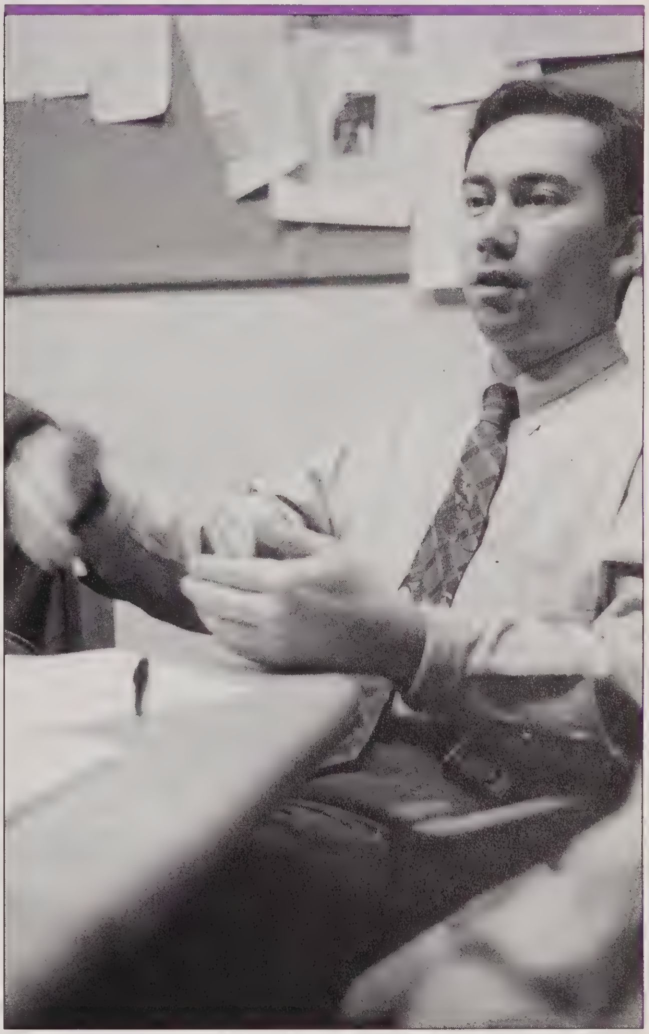
One of their recent studies reanalyzed information from a major clinical AZT trial in a way that asked whether administering the drug to symptom-free people produced a benefit that outweighed any side effects. Their results, published in the *New England Journal of Medicine*, found that the quality-of-life benefits of AZT — measured as time without symptoms — were essentially balanced by reductions in quality of life due to side effects.

"There is a tradeoff involved in taking AZT, between delaying disease progression and increasing side effects," says Dr. Lenderking. "This points out the importance of considering the patient's preferences before starting drug therapy. One person may want to stay free of unpleasant side effects for as long as possible and choose to hold off taking AZT. Another may prefer to tolerate side effects to delay disease symptoms."

"More recent studies suggest that even delaying symptoms does not result in longer life, so quality-of-life discussions are paramount to making the decision to start AZT," he adds. The next step in this work will be adapting the quality-of-life-measurement studies as tools that can help individuals and their doctors make these decisions, and can measure the results of clinical drug trials.

While more effective treatments for the physiological effects of HIV remain elusive, the staff of the Andrews Unit is helping people with HIV maintain their psychological well-being, individual and social supports, and overall quality of life.

"It is very difficult," says Dr. Savage, "to work with people whom you know, and they know, are dying — and for whom there's not a lot you can do. But the fact that people with HIV are living longer is one ray of hope. Helping them maintain the best possible quality of life during that time is one way we can really make a difference." ■


*Dr. Jonathan Worth*

# *New nursing leader seeks to broaden opportunities*

*Dr. Gail Kuhn Weissman*

"WE CAN LOOK at the impact of health care reform on nursing as an opportunity to correct things we have been dissatisfied with in the existing system," says Gail Kuhn Weissman, EdD, RN, the new leader of the MGH's Department of Nursing.

Dr. Weissman, who became Associate General Director and Chief Nurse Executive earlier this year, sees the hospital's vision of creating a broad-based health care system, in partnership with its new affiliate Brigham and Women's Hospital, as an opportunity for MGH nurses to put their skills to use in new ways.

"In the past, the health care system tended to pigeonhole people and the way care is provided. Those who aren't afraid of changes — who are willing to take risks, demonstrate flexibility, and see a vision of a better health care system — will do well as the system evolves," she notes.

Dr. Weissman came to the MGH from Mt. Sinai Medical Center in New York, where she spent more than 20 years as Director (later Vice President) of Nursing and Dean of the School of Continuing Education for Nursing. Showing her enthusiasm for her move to the MGH, she says, "The MGH is an exciting, dynamic place. There is incredible brilliance here, and people's minds are never still. There is a love and pride in the hospital among the people who work here — in all areas."

In her role as a senior administrator, Dr. Weissman will influence the hospital's restructuring of patient care at all levels. "We want to create a program that makes changes to the health care system unnoticeable to patients, at any point in their care," she says.

Part of this effort will be increased integration of patient services. In this approach, nurses, physicians, and other health care professionals form interdisciplinary teams addressing patient needs, instead of focusing their efforts only on the concerns of their particular discipline.

Another priority will be the creation within the Nursing Department of a Center of Life Work, a resource to help nurses learn new ways to apply their skills in a changing environment.

"The center will help nurses maximize their strengths and be prepared to move throughout the new mix of health care delivery settings," she explains. "If an inpatient floor must close because fewer patients are admitted, we want to be able to retain the expertise of those nurses whenever possible. To do that we must be creative and look beyond the inpatient units to the total health care system we are establishing."

In addition to her positions at Mt. Sinai, Dr. Weissman also held nursing leadership roles at Montefiore Hospital and Medical Center in New York. She has participated in several international projects — traveling to Africa, China, Chile, and the Dominican Republic to speak, teach, and share her experiences with colleagues from around the world. A fellow of the American Academy of Nursing, she is the author of numerous papers and articles and has served on the editoral boards of several nursing publications.

> ***Those who aren't afraid of changes — who are willing to take risks, demonstrate flexibility, and see a vision of a better health care system — will do well as the system evolves."***

Dr. Weissman is a graduate of Vanderbilt University School of Nursing and received master's and doctoral degrees from Columbia University Teachers College. She also has been named a professor at the MGH Institute of Health Professionals.

"The MGH has always been on the cutting edge. That's one of the reasons people choose to work here," she says. "We can change with the times, take the lead in what health care delivery will look like, and still maintain the hospital's preeminence. If we can't do it, nobody can." ■

# A revolution in ulcer treatment

IT DOES NOT happen very often that the thinking about the cause and treatment of an illness makes a complete turnaround. But that is what has happened with ulcers.

During the 1970s, it seemed clear that peptic ulcers were caused by either excessive secretion of stomach acid or a breakdown in the natural systems that protect the stomach lining from acid. The newest, most effective ulcer drugs blocked the process by which acid was released into the stomach. Similarly, surgical procedures which were used for the most severe ulcers, focused on the acid-producing mechanisms.

But in 1982 a group of Australian researchers made a startling claim, that ulcers were actually caused by infection with a newly identified bacteria. They found this organism, which they called *Helicobacter pylori*, present in the stomach lining of more than 90 percent of patients with duodenal ulcers (ulcers in the first portion of the small intestine) and about 80 percent of patients with gastric (stomach) ulcers.

"Most US specialists initially were very skeptical of this theory in the mid 1980s," says Timothy Wang, MD, an MGH gastroenterologist. "Many of them had been working to advance the acid theory over previous beliefs that stress or dietary factors caused ulcers. And therapeutic drugs such as cimetidine and ranitidine were extremely effective for healing peptic ulcer disease. But subsequent investigations [including some MGH studies] confirmed the Australian group's findings that *H. pylori* was present in most patients with ulcers. In the past few years, more and more people have been won over."

The strongest support for the new theory came in February when a panel of independent experts convened by the National Institutes of Health endorsed the use of antibiotics and other bacteria-killing drugs in ulcer treatment. Daniel K. Podolsky, MD, Chief of the MGH Gastrointestinal Unit and a member of that panel, called the recommendation "an important sea change in ulcer treatment policy."

While treatment based on acid-reducing medication was usually successful in relieving the pain associated with ulcers, it rarely solved the problem permanently. Symptoms eventually returned for almost all patients, sometimes striking without warning. Some patients kept taking the drugs for years to avoid a recurrence.

The therapy recommended by the NIH panel — several combinations of anti-bacterial drugs supplemented with bismuth (the active ingredient in Pepto-Bismol) or an acid-blocking drug — has been shown in numerous studies to stop ulcer symptoms after a single course of treatment for most patients. Overall, less than 10 percent of patients had a recurrence of symptoms within two years of anti-bacterial treatment, compared with more than half the patients receiving acid-fighting drugs alone.

> ***Overall, less than 10 percent of patients had a recurrence of symptoms within two years of anti-bacterial treatment, compared with more than half the patients receiving acid-fighting drugs alone.***

While the recommendations are expected to apply to almost all ulcer patients, the NIH panel stressed that infection with *H. pylori* must be confirmed before initiating anti-bacterial treatment. Occasionally ulcers may be caused by something else: taking large amounts of anti-inflammatory drugs like aspirin or ibuprofen, conditions such as Crohn's disease (which usually affects the intestines), and some rare genetic conditions.

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"It is generally necessary to do an endoscopic examination of patients with symptoms suggesting ulcer disease," says Dr. Wang. An endoscope is a tube passed down the esophagus, through which a physician can observe the stomach and take tissue samples for testing. Researchers are working on less invasive ways to diagnose the bacterial infection, including blood or breath tests, but none have yet received FDA approval.

There are many questions about the role of *H. pylori* in ulcer disease that need to be answered, Dr. Wang adds, starting with how the infection actually leads to ulcer development. "We know that helicobacter infects the stomach — although exactly how it is acquired is uncertain — and basically hides in the stomach lining. It's very well adapted to that location, because it produces an enzyme that protects it from the very acid environment.

"But the most common ulcers caused by helicobacter are in the duodenum, and you often don't even find the bacteria there. So we don't know if the infection makes the stomach generate more acid or causes less resistance to acid's effects, or something else. It's a complicated issue."

Another complication is that, although more than 20 percent of the US population is infected with *H. pylori*, the vast majority of infected people never develop ulcers. Although almost all those with *H. pylori* do have gastritis (inflammation of the stomach), most of them remain symptom-free.

> *In the less developed countries of the world, stomach cancer occurs much more frequently. If large-scale studies show that eradication of* H. pylori *can prevent stomach cancer, anti-bacterial treatment could have an important public health impact worldwide.*

One of the most recent clues is the discovery that *H. pylori* tends to invade cells displaying an immune-system signal associated with type O blood, which fits the established observation that ulcers are more common among that blood type. The identification of other such infection targets, as well as genetic or behavioral factors that may contribute to ulcer development, could help solve the mystery.

Another crucial area of investigation is the possible relationship between *H. pylori* and stomach cancer. Several studies have suggested that those with the infection are up to four times more likely to develop stomach cancer. The incidence of stomach cancer has declined in this country in recent years, which may relate to a declining rate of infection with *H. pylori*. Infection with *H. pylori* is much less common among younger Americans than those over 60.

In the less developed countries of the world, where *H. pylori* infection is quite common, stomach cancer occurs much more frequently. If large-scale studies show that eradication of *H. pylori* can prevent stomach cancer, anti-bacterial treatment could have an important public health impact worldwide.

"Gastric [stomach] cancer is probably the second or third most common malignancy worldwide," Dr. Wang says. "At some point in the future, we may find evidence to support treating almost everyone with helicobacter infection to prevent cancer. But right now we simply don't know enough to make that recommendation." ■

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# MGH News

Massachusetts General Hospital, Boston, Massachusetts
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*Dr. Warren M. Zapol*

# Dr. Zapol is new Anesthesia Chief

The new Chief of the MGH Anesthesia Service has pursued his interests in the respiratory system to some of the remotest spots in the world. And in the more familiar venues of the operating room and research lab, Warren M. Zapol, MD, has participated in discoveries that have already saved lives and may revolutionize treatment of critically ill infants and adults.

An MGH staff anesthesiologist since 1972, Dr. Zapol says of his new appointment: "It's very exciting and challenging; this is one of the biggest departments in the country. We do a lot of clinical anesthesia, and we do it very well."

Dr. Zapol succeeded Richard J. Kitz, MD, who has stepped down after 25 years as service chief *(see page 4 story)*. "Warren is a person of international reputation, an outstanding critical care physician who also does research that nobody else is doing," Dr. Kitz says. "He's perfect for the MGH, and I'm overjoyed to have him as my successor."

The discipline of anesthesiology involves much more than administering drugs that alleviate pain or render patients unconscious during a surgical procedure. Anesthesiologists control all of a patient's vital functions during an operation. Their expertise is called on in recovery rooms and intensive care units where critically ill patients require precise monitoring and high-technology support.

### *New drugs give flexibility*

Dr. Zapol explains that some of the newest drugs are giving anesthesiologists more flexibility and control than ever before. "We still don't have the ideal anesthetic, but there is a general trend to use more intravenous agents," he says. "With inhaled anesthetics there is a lag between when we turn off the gas and when we see a response in the patient. But we can turn some intravenous agents on and off and see patients' responses change almost instantly. And new

*(Continued on Page 2)*

## *Few patients plan for end-of-life decisions*

When former President Nixon's condition began to deteriorate after his stroke, his doctors tried several techniques to reduce the complications that eventually led to his death. One thing they did not do, according to news media reports, was place Mr. Nixon on a respirator. Apparently the former president had expressed a desire to avoid such "heroic means" if they were required to maintain his life.

Despite all the attention paid to issues surrounding end-of-life decisions, patients like Mr. Nixon, whose preferences are known to their families and health care providers, remain in the minority. Surveys have shown that only 20 to 25 percent of adult Americans have completed a formal statement outlining their preferences or designated a proxy (a legally recognized replacement) to make decisions about care if they are unable to do so.

Linda L. Emanuel, MD, PhD, an MGH internist, has been a national leader in studying and creating ways to help patients indicate their wishes for the types of medical treatment they might receive. She and her husband — Ezekiel J. Emanuel, MD, PhD, an oncologist at Dana-Farber Cancer Institute — put

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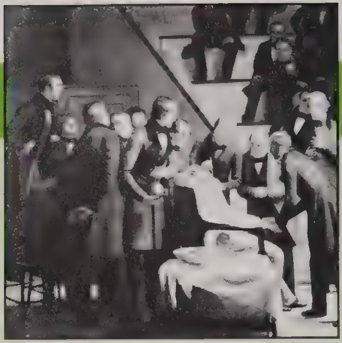

## A Medical Maverick

OLIVER COPE, MD, who died on April 30 at the age of 91, never hesitated to challenge the accepted practices of his day. Spending his entire medical career of more than 60 years at the MGH, he first made his mark as a surgeon of the endocrine system and pioneered treatment of diseases of the parathyroid glands.

In 1942, after the attack on Pearl Harbor, Dr. Cope was invited to join a government panel reviewing emergency medical procedures, including burn treatment. In preparation for the meeting, he immersed himself in literature about burns and began to question current practices. Although a newcomer to burn treatment, he recommended an alternative therapy to the panel and returned to the MGH with a grant to test his ideas.

Ten months later, Dr. Cope's techniques received a true baptism of fire when more than 100 victims of the Cocoanut Grove disaster were brought to the MGH. The successful outcomes led to the adoption of Dr. Cope's methods by the armed forces, which saved countless lives during World War II. Dr. Cope's continued interest in burn treatment led to the establishment of the Shriners Burns Institute in Boston.

Dr. Cope also was among the earliest advocates of incorporating knowledge from the behavioral sciences into medical education and practice. An inspiring teacher to generations of MGH residents and Harvard medical students, he twice served as Acting Chief of the MGH Surgical Services. But probably his greatest battle was to change his colleagues' thinking about breast cancer treatment.

Embarking on a controversy that raged for years, Dr. Cope was among the first surgeons in this country to treat breast cancer by removal of only the tumor, followed by radiation. Papers he wrote or presented—with MGH colleagues from oncology, pathology, and radiation therapy—were rejected by prestigious medical journals. When the *Radcliffe Quarterly* finally ran an article on Dr. Cope's work in 1970, it was immediately reprinted by leading women's magazines, and within weeks he was swamped with letters from women around the country.

More than 30 years after Dr. Cope stopped doing radical mastectomies, his ideas are largely accepted by the cancer community. Typically, he gave credit for his work to the women who impressed upon him the impact that breast loss and disfigurement had on their lives.

In the words of Paul S. Russell, MD, former Chief of the MGH Transplant Unit, Dr. Cope was "a towering figure at the MGH and in the world of surgery at large." As a teacher, researcher, and clinician he never lost sight of his primary goal: to relieve the suffering of his patients. ■

## —Dr. Zapol

*(Continued from Page 1)*

computerized intravenous pumps allow us to mix and match the right drugs for each patient's needs."

The search for even better anesthetic drugs will depend on improved understanding of the nervous system, he adds. "We need to further increase our ability to control pain, which is what anesthesia is all about. One of my priorities will be to assemble a team to study the nervous system and develop new anesthetic agents based on the latest knowledge."

### *Minimizing operating room delays*

Another focus will be improving efficiency in the operating room, one of the most costly, resource-intensive areas of any hospital. Here one of the most effective strategies could be one of the most basic: making sure procedures start on time and minimizing delays in the course of an operation.

Central to Dr. Zapol's plan will be a new computer network connecting staff anesthesiologists with the operating rooms. Information will be compiled on every step in patients' surgical experiences—from arrival at the hospital to release from the recovery room—with the goal of finding where delays occur and how they may be eliminated.

"So many people are involved in the operating room—surgeons, nurses, anesthesiologists, and technicians—and coordinating their time and effort is

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PHOTOGRAPHS: Pages 1, 6, Susan McGreevey; page 3, Dr. Jesse Roberts; page 4, Joshua Touster; page 7, facial expression photos by Dr. Paul Ekman, courtesy of Dr. Nancy Etcoff.

incredibly complex. Understanding how all their efforts fit together and identifying areas where time may be wasted could really cut costs," he says.

### *Mysteries of the diving reflex*

Dr. Zapol's interest in the respiratory system has taken him to such unlikely locations as the rugged coastline of Korea and the ice sheets of Antarctica for studies of the diving reflex. This physiological response — which includes a cessation of breathing, slowing of the heart rate, and constriction of blood vessels — is produced when any mammal places its face in cold water.

Along with several colleagues, Dr. Zapol has investigated how the diving reflex operates in the champion divers of the animal kingdom, the Weddell seals of Antarctica. These animals, which can stay under water as long as 93 minutes, have an unusually large and oxygen-rich blood supply. It also appears that the animals' spleens act as internal oxygen tanks, contracting to push more blood cells into the bloodstream during dives.

Several of the same properties, on a much smaller scale, have been seen in Korean *ama* (sea women), who also have been studied by Dr. Zapol's group (*MGH News*, December 1989). These women, who harvest shellfish from the sea bottom, hold their breath for as long as 90 seconds and dive repeatedly for up to four hours daily. Ultrasound studies by William E. Hurford, MD, Director of the MGH Respiratory Intensive Care Unit, showed that the women's spleens contract during diving, and blood tests revealed increased levels of oxygen-carrying red cells.

Dr. Zapol explains that the *ama*, as well as a group of Japanese women who use different diving techniques, have trained their bodies to conserve oxygen in an extreme environment by partially mimicking the physiological changes seen in the seals. While his new responsibilities will prevent him from returning to these remote regions, Dr. Zapol notes that several MGH staff members are eager to continue the studies.

*Taking a break from his studies of the Weddell seals in Antarctica, Dr. Warren Zapol gets acquainted with another local resident.*

### *Life-saving research*

Early in his career, Dr. Zapol helped to refine techniques of extracorporeal membrane oxygenation (ECMO), in which an external machine acts as an artificial heart and lung. ECMO, which replenishes oxygen in the bloodstream of patients with serious, acute lung problems, has proved particularly useful in treating newborn infants with life-threatening respiratory ailments.

Most recently Dr. Zapol has helped to define how the common gas nitric oxide (not to be confused with nitrous oxide, or laughing gas) affects the respiratory system. One of the most hotly researched substances of recent years, nitric oxide plays critical roles in the immune and nervous systems. In blood vessels, nitric oxide relaxes surrounding muscles, which opens up the vessels and reduces blood pressure.

Dr. Zapol and his colleagues realized that nitric oxide could be ideal for treating several conditions in which the flow of unoxygenated blood into the lungs is impaired. Other medications to open constricted lung blood vessels act throughout the body, causing a drop in blood pressure that could cause shock in a critically ill patient. But when inhaled in tiny doses, nitric oxide gas dilates only those blood vessels directly supplying the lungs.

MGH researchers — including Jesse D. Roberts, MD, a neonatologist and anesthesiologist — were the first to test nitric oxide for persistent pulmonary hypertension of the newborn (PPHN). In this potentially fatal condition, the marked increase in blood flow to the lungs that normally follows birth does not occur. Inhaled nitric oxide treatment has successfully, sometimes dramatically, reversed PPHN (*MGH News*, April 1993), and studies confirming its effects are going on around the world.

"Research into inhaled nitric oxide is really booming," Dr. Zapol says. "More than 100 centers in this country are investigating its use, and there are a half-dozen randomized trials in North America and Europe. If these studies confirm our results — and preliminary reports are very promising — nitric oxide gas may someday be a standard supply item in every delivery room."

Working with Dr. Hurford, Luca M. Bigatello, MD, anesthesiologist, and Robert Kacmarek, PhD, Chief of Respiratory Therapy, Dr. Zapol has also investigated nitric oxide to treat adult respiratory distress syndrome, in which portions of the lung become clogged with fluid and debris after a serious injury or infection. Initial studies, in collaboration with German researchers, indicate that the gas could be an ideal treatment for this life-threatening complication.

"The nitric oxide studies have gone beautifully, and I'm thrilled we've already saved lives of babies and adults with respiratory failure," Dr. Zapol says. "Now I'm looking forward to nurturing the careers of others who will advance anesthesia and intensive care."

Dr. Zapol is a graduate of MIT and the University of Rochester School of Medicine. After a surgical internship at Boston City Hospital, he completed a research fellowship at the National Heart and Lung Institute and an anesthesia residency at the MGH. He is also the Reginald Jenney Professor of Anesthesia at Harvard Medical School. ■

# Dr. Kitz helped transform the image and practice of anesthesiology

In looking back over his quarter century as Anesthetist-in-Chief at the MGH, Richard J. Kitz, MD, sees a tangible legacy of his leadership. "More professors and chiefs of anesthesia departments have trained at the MGH than at any other program in the country," he says with understandable pride.

While such a record may be expected at the institution where the medical use of anesthesia began *(see sidebar),* it is also a product of goals Dr. Kitz set for his department when he became chief in 1969.

"Getting people into anesthesia was tough back then. It was not a popular career choice," he explains. "In those days, the general attitude among medical school professors, who had a lot of influence over students' career choices, was that anesthesia was just 'putting people to sleep.' That had been true at the time those professors trained, but we were already branching out into the areas of pain management, respiratory care, and critical care."

### *Attracting the best*

Dr. Kitz and the MGH Anesthesia Service took the lead in a nationwide effort to bring more top-quality medical school graduates into anesthesia. "I capitalized on the fact that our Respiratory Intensive Care Unit, the first one in use anywhere, was established by anesthesiologists. We created some special opportunities for medical students to spend time there and see the kind of work we were doing. They would have a good experience, go back and tell their colleagues about it, and interest grew."

Taking a similar long-range approach to building a department that would attract talented medical graduates to the MGH Anesthesia Service, Dr. Kitz concentrated on building up the residency program and recruiting young physicians who could be the leaders of tomorrow. And after choosing residents and young staff members who showed outstanding leadership qualities, Dr. Kitz developed an environment that encouraged creativity and exploration.

### *Freedom to explore*

For example, within an overall program that provides a complete grounding in the science and practice of anesthesia, residents were given the freedom to pursue independent, often interdisciplinary, projects and access to resources needed for such activities.

Warren M. Zapol, MD, who succeeded Dr. Kitz as chief, says: "My career is an example of the kind of independence Dr. Kitz has given people. I've pursued research projects that have taken me to Japan, Korea, and Antarctica *(see page 1 article).* I can't imagine having had as much freedom from anyone else."

George E. Battit, MD, Clinical Director of Anesthesia, adds, "One of his basic philosophies — and he really lived up to it — was that he worked for us, the staff members, and not that we worked for him."

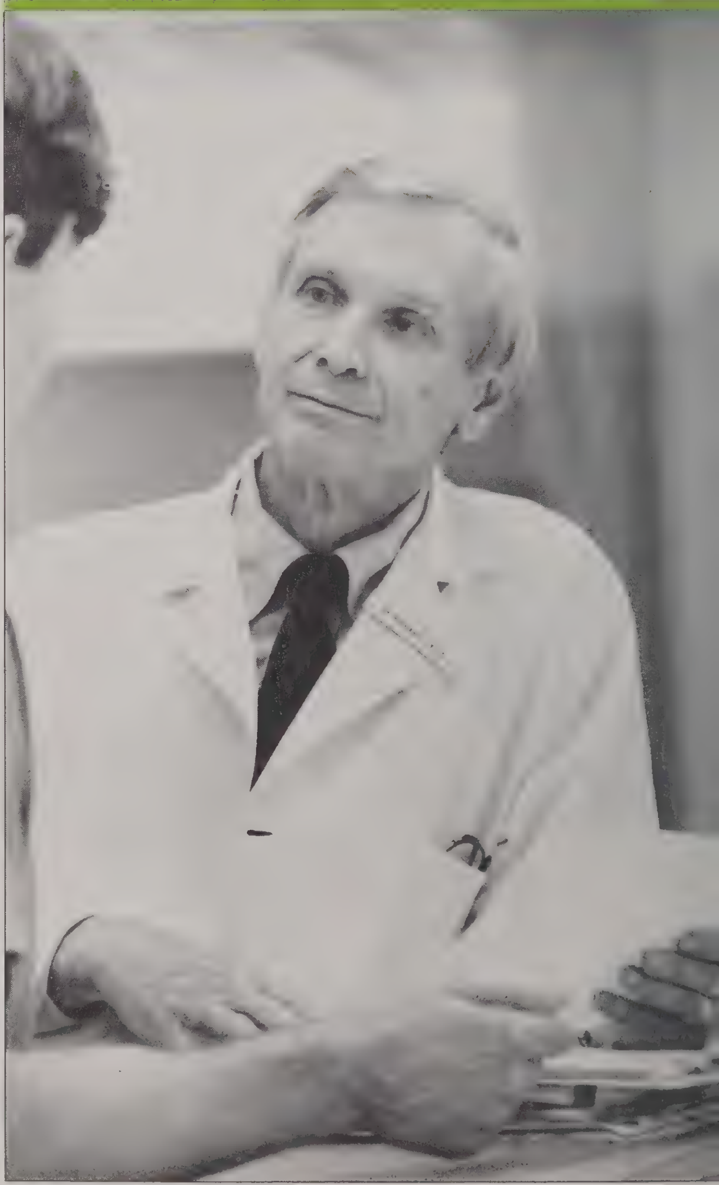
Another example of Dr. Kitz's impact is described by Jeffrey B. Cooper, PhD, Director of Anesthesia Technology and Biomedical Engineering. "He brought a group of engineers like me into the department to help develop new technology, but he also allowed us to do our own thing."

In Dr. Cooper's case, freedom led to studies of human error and its role in anesthesia-related mistakes. That work set the stage for an international movement addressing anesthesia safety and the establishment of the Anesthesia Patient Safety Foundation, co-founded by Dr. Kitz and Cooper, and Ellison C. Pierce, MD, of the Deaconess Hospital.

### *Advances in safety*

Much progress in patient safety has come in two areas Dr. Kitz has championed: pharmacology, the development of safer, more effective anesthetic drugs, and computerized monitoring systems. Dr. Battit explains: "Dr. Kitz devoted a lot of time to research into new drugs that block neuromuscular pain signals. He also brought in Dr. Keith Miller who has done some very basic research studies on the mechanisms of anesthesia."

A recent extension of high-technology monitoring is development of an anesthesia simulator, a machine that recreates the experience of delivering anesthesia in an operating room for training purposes (*MGH News*, January-February 1993). The anesthesia departments of the five Harvard teaching hospitals have now jointly acquired a simulator.



*Dr. Richard J. Kitz*

"The simulator is the next major move in the education of residents and the continuing education of practicing anesthesiologists," Dr. Kitz says. "There are rare problems in anesthesia that most clinicians may only see once in their careers. But they'd better be ready for them when they happen, or a patient's life could be at stake. By regularly rehearsing such events on a simulator — just like airline pilots do — they can be prepared for those unusual challenges."

For residents, the simulator offers the opportunity to practice delivering anesthesia in both routine and complicated situations before their first genuine operating-room experience.

### *Integrating medicine and technology*

Another way Dr. Kitz has worked to integrate medical science with high technology is his more-than-20-year involvement with the Harvard Medical School/Massachusetts Institute of Technology Division of Health Sciences and Technology (HST). The program, which Dr. Kitz co-directed for six years, is designed to bring college graduates in such fields as engineering, chemistry, physics, and mathematics into the medical sciences. HST students have access to resources of both institutions and may work toward MD, MS, PhD, or combined degrees.

"Among the goals of HST is to produce cardiologists who comprehend fluid mechanics, orthopedic surgeons who have mechanical engineering skills, and anesthesiologists who understand how computers acquire, process, and display biologic signals," he says.

Dr. Kitz says he believes that some degree of the broad-based grounding in medicine and technology exemplified by the HST program will be essential to developing the anesthesia leaders of the future. With the specialty now fully recognized for its essential role in the most intricate aspects of medicine, he sees the reliance on high technology as an attraction to computer-sophisticated medical students. But he emphasizes that all the equipment and machines are there to provide the best in patient care.

"We couldn't do what we do without technology," he says. "The anesthesiologist maintains the life of the patient while the surgeon intervenes in a disease process. We seize control of patients' vital functions — consciousness, breathing, heart rate, muscle activity — their lives are in our hands."

## *Their eyes were on the prize*

A way to eliminate the pain of surgery was one of the eagerly-sought prizes of mid-19th century medicine. And the eventual discovery and demonstration of ether anesthesia sparked a controversy that was as bitter as any contemporary scientific dispute.

Throughout history, surgery had been a last resort. Patients had to be held or strapped down against the pain. Speed was one of the surgeon's greatest skills. Narcotic drugs and alcohol could dull the senses, but they were only partially effective and had dangers.

The gaseous drugs ether and nitrous oxide had been used to treat lung diseases and, perhaps most commonly, as recreational drugs. Several physicians participated in "ether frolics," and some noticed that participants who bruised or injured themselves while under the drug's influence felt no pain.

Georgia physician Dr. Crawford Long was probably the first to use ether during an operation, but he did not report or publish his experiences for several years. Connecticut dentist Dr. Horace Wells used nitrous oxide when extracting teeth, but his attempt to demonstrate the technique to a group of Harvard physicians, including MGH co-founder Dr. John Collins Warren, failed when he gave the patient an insufficient dose.

It was Boston dentist Dr. William T.G. Morton, a former student and partner of Dr. Wells, who convinced Dr. Warren to let him demonstrate the drug he had been using for painless extraction, a substance he called letheon. On October 16, 1846, in the operating theater at the top of the MGH's Bulfinch Building, Dr. Morton administered the drug to patient Gilbert Abbott. Dr. Warren proceeded to remove a tumor from the patient's neck. When the patient awoke and reported feeling no pain, Dr. Warren pronounced, "Gentlemen, this is no humbug."

Dr. Morton had tried to keep the identity of his drug a secret, hoping to reap the profits of its use. But after several successful painless surgeries, the MGH staff refused to use it until Dr. Morton revealed its identity. He finally relented: "Letheon" was ether.

Within weeks of the ether demonstration, MGH surgeon Dr. Henry Bigelow reported the success at scientific meetings and published a paper in the precedessor to *The New England Journal of Medicine*. While some doubted the claims or insisted that such practices were contrary to God's law, surgeons around the world began using ether and later nitrous oxide, chloroform, and other inhaled drugs to eliminate surgical pain.

But public accolades also brought out rival claimants. Dr. Long finally published reports of his operations, along with a sworn statement from a patient as to the date and use of ether. Dr. Wells also claimed a share of credit for the discovery.

Perhaps most bizarre was Dr. Charles Jackson, a Boston physician and chemist who had advised Dr. Morton in his early experiments with ether. Dr. Jackson shared in the patent issued for the technique, but as interest in the use of ether grew, he began claiming a larger and larger role, finally asserting that it was all his idea and that Dr. Morton simply carried out his instructions. (Dr. Jackson had a history of making such claims. He also tried to take credit for Samuel Morse's invention of the telegraph).

The controversy raged for years, even being argued before Congress. By 1880 all of the disputants were dead; none of them had gotten rich from the "discovery" of ether anesthesia. The real beneficiaries were the surgeons, who now could apply their techniques to previously unapproachable problems, and the patients, who were finally released from the pain of surgery.

*(Continued from Page 1)*

together the medical directive, a tool that allows patients to designate specific treatments they would or would not want to receive in several possible situations (*MGH News*, January 1990).

"It's normal for people to avoid discussing issues related to their deaths," says Dr. Emanuel. "In fact, only 50 percent of patients have made estate wills disposing of property. When we ask people why they haven't made plans, they say things like they're not old enough, not sick enough, or they'll know when the time is right to do something. That indicates a lot of very natural denial."

Actually patients' most frequent answer to why they have not made an end-of-life plan is that their doctor did not broach the subject with them. Again, Dr. Emanuel explains, that is not surprising.

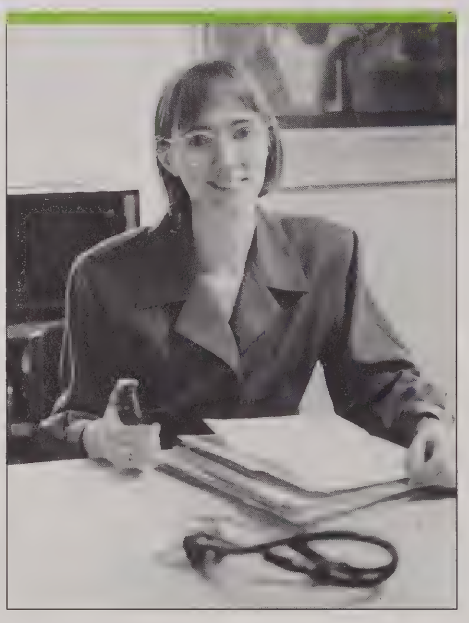
"For many physicians, discussing and planning for a patient's eventual death seems almost a betrayal of their beliefs. They were trained to treat illness, eliminate pain, and do whatever was necessary to prevent death," she says. "It's understandably difficult to see discussing death and dying as part of the physician's role. However, society wants us to do this, and as a profession, we are becoming more comfortable with helping our patients make these decisions."

Dr. Emanuel adds that documents like the medical directive, which explicitly spells out possible situations *(see sidebar),* are a useful worksheet for patient-physician discussions. Physicians can explain the appropriate uses of various treatments and clear up misconceptions. Even patients who may originally be hesitant to discuss the subject are often relieved to get the issues in the open and reassured to know that their wishes will be followed. It can also be a welcome assurance that they will not be abandoned by their physicians and family members.

"Completing a medical directive is not nearly as time consuming as people think," she says. "It takes about 15 minutes for a doctor to initially pencil in a predrafted document with a patient. At home patients can use that framework to firm up their decisions, and five minutes at a follow-up visit is usually enough to review the document and answer remaining questions."

Dr. Emanuel says she believes that the medical directive has several advantages over other techniques currently used to guide end-of-life decisions. While so-called living wills have been in use more than 15 years and are legally endorsed in most states, they have tended to oversimplification, for instance directing that no artificial means be used to prolong life when there is no hope of recovery. Such blanket statements often do not clearly apply to a particular patient's circumstance.

Not only does the medical directive cover a broader range of situations, but a study published earlier this year by the Emanuels and their colleagues indicates that a careful review of situation- and treatment-specific choices made in the directive can infer a patient's probable preferences in other circumstances. Another recent study found that those completing a medical directive change their minds relatively little when surveyed up to two years later.



*Dr. Linda Emanuel*

Another common mechanism for addressing these decisions is designation of a health care proxy, someone (often a family member) who can make decisions for an incompetent patient. But several studies have shown that proxies' knowledge of patients' treatment preferences was surprisingly poor, little better than would be achieved by random guessing.

In addition, the responsibility of making such decisions — especially discontinuing life-sustaining treatment — can be emotionally overwhelming for a proxy. Dr. Emanuel notes that completion of a document like the medical directive can help proxies discuss decisions with a patient's doctor and can reassure them that they are indeed doing what the patient would have wanted.

And "doing what the patient wanted" is the ultimate goal of the medical directive, Dr. Emanuel explains. "We cannot know the wishes of someone who is no longer capable of having a wish," she says. "Instead we can only know what the person wanted in advance and try to ensure that a patient's surviving interest — the same concept that underlies estate wills — is honored."

## *Medical directive emphasizes choice for patients*

THE MEDICAL DIRECTIVE created by Linda L. Emanuel, MD, PhD, MGH internist, and Ezekiel J. Emanuel, MD, PhD, Dana-Farber Cancer Institute oncologist, describes six different possible situations that may result in the need to make treatment decisions for an incompetent patient. These include irreversible coma; combinations of serious brain damage and terminal illness; brain damage without terminal illness; and life-threatening but possibly curable illness.

For each of these situations, patients can indicate their desires regarding six types of treatment ranging from pain medications and antibiotics to mechanical breathing and cardiopulmonary resuscitation. Patients can indicate that they want the treatment, do not want the treatment, or are undecided. They can also indicate that the treatment should be tried and, if unsuccessful, stopped.

In addition, patients can designate the overall goal of treatment in each situation: to prolong life, to attempt to cure, to choose quality of life over longevity, or to provide comfort care only. The form also allows for the designation of a health care proxy, preferences regarding organ donation, and any other statements the patient would like to add.

Copies of the medical directive are available from The Harvard Medical School Publications Group, PO Box 380, Boston, MA 02117.

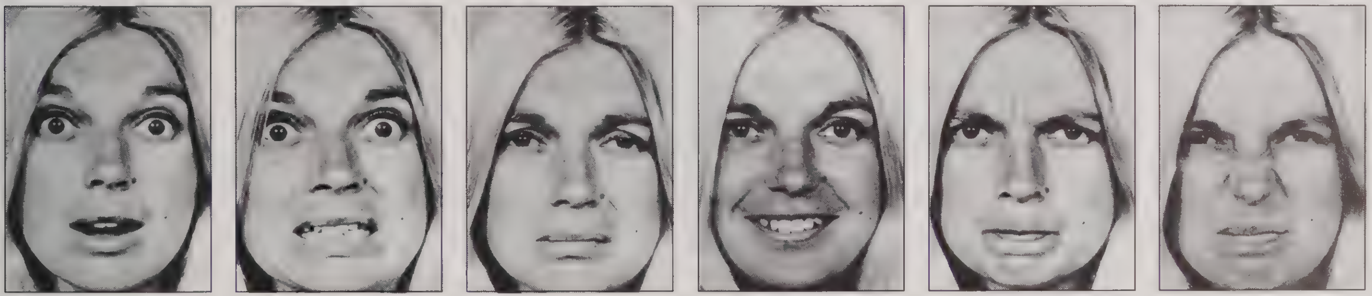
Dr. Emanuel, who also is Assistant Director of the Division of Medical Ethics at Harvard Medical School, says that the current controversy over medically assisted suicide, personified by Dr. Jack Kevorkian, confuses and misleads people into thinking that prolonged suffering or a quick death are their only choices. She recalls an occurrence from early in her career involving a patient being treated for breast cancer.

"She wanted me to agree to help her die if her cancer returned. Instead we reviewed an early version of the medical directive. The opportunity to discuss so many options and make her own choice was a relief, and assisted suicide became an irrelevant notion for her," Dr. Emanuel says. "I really think that the work we are doing in this area is an antidote to Dr. Kevorkian."

# As clear as the look on your face

THE HUMAN FACE: For most of us, it is the most potent symbol of who we are. We use it to express a full range of emotions, and we gather important clues about human interaction by reading the faces of those around us. Even infants are fascinated by faces and will intently stare at the simplest representation of the familiar eyes, nose, and mouth.

Many scientists now believe that the abilities to associate a face with a particular individual or interpret facial expressions are preprogrammed into the human brain, and studies have shown that certain facial expressions are universally associated with particular emotions in cultures worldwide. *(see photos below)*



*Researchers have found that people around the world recognize the emotions expressed in these typical facial expressions: (from left) surprise, fear, sadness, happiness, anger, and disgust.*

Nancy L. Etcoff, PhD, an MGH neuropsychologist, studies how the face is used to transmit social and emotional signals, what parts of the brain are involved, and how patients with brain injuries can lose these abilities that most of us take for granted.

"No one teaches us how to recognize an emotion, but we do it all the time, often unconsciously," she says. "We've all had the experience of talking with someone and, afterwards, feeling that something was not quite right about the conversation. If you carefully watch a videotape of that interaction, you might see subtle facial clues to emotions totally different from what that person was saying."

But in real life, those facial clues are often missed, as shown in one of Dr. Etcoff's recent studies, conducted in collaboration with Paul Ekman, PhD, from the University of Calfornia at San Francisco. Volunteers viewed videotapes of nurses who spoke of looking at a beautiful scene. Some of those nurses actually were looking at very unpleasant pictures, but they had been instructed to mask any feelings of sadness or disgust.

In almost all cases, Dr. Etcoff says, volunteers were unable to tell which nurses were lying and which were telling the truth, even though close examination revealed identifiable cues in the facial expressions and vocal tones of those looking at unpleasant images. In repeated tests with people who might be expected to detect lying—judges, psychiatrists, and FBI agents—the results were the same.

Only Secret Service agents were able to see the difference. Dr. Etcoff explains: "A major part of their job is to scan a crowd, looking for people who might cause trouble. They have to be able to identify people's emotions by facial expression."

What accounted for this difference? The researchers wondered whether those viewing the tapes paid more attention to the nurses' words than to their expressions. They tested this theory with a group of patients who had lost the ability to understand spoken language because of a stroke or head injury. Like the Secret Service agents, these patients were much more accurate at detecting what the nurses were feeling and when they were lying.

"When it comes to perceiving emotion, we seem to believe what we hear more than what we see," Dr. Etcoff says. "But it's fascinating to see how that tendency can be changed by training or necessity."

Evidence that recognition of faces is a discrete ability, separate from general learning skills, comes from studies of brain-injured individuals who have lost all or part of that ability. Dr. Etcoff describes one long-time patient who was in an automobile accident more than 20 years ago.

"To him, faces look like illegible handwriting," she explains. "He says it's like looking at words, knowing that they're words, and having no idea what they mean. He's able to do almost everything else. He can recognize objects; he can distinguish between different types of patterns; and he can recognize gender and facial attractiveness. But he cannot match faces with people's identities, even his own."

The techniques used to compensate for such a loss also show how specific the facial-recognition ability is. This patient uses voices, clothing, hairstyles, and even posture to recognize people and has built himself a successful life with family and career. But, Dr. Etcoff explains, the loss

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of such abilities can be a profound handicap in interpersonal relationships.

"Patients who cannot decode facial expressions may have subtle social problems that bring them in for counseling. They may originally be diagnosed as depressed because they don't even realize why they feel out of step with the people around them," she says. "Other brain-injured patients may have trouble expressing emotions facially or through their voices. We worked with a teacher who couldn't control his class because he said everything in a monotone. Not only did he sound boring, but he couldn't convey 'I mean business now' to his students unless he explicitly told them what he meant."

Correlation of these signaling and recognition abilities with specific sites in the brain has so far proven difficult because many of the patients studied have injuries in several areas. It does appear, however, that facial recognition is primarily located on the right side, which is generally regarded as more visually oriented, and largely in the temporal (behind the temples) area.

"There's tremendous controversy right now as to whether there's any part of the brain absolutely dedicated to faces," Dr. Etcoff says. While animal studies have suggested that certain brain cells respond selectively to faces and others to facial expressions, few investigations have been done in humans.

One possible future avenue would be collaboration with neurosurgeons treating patients with conditions, like intractible epilepsy, for which the only remedy is destroying malfunctioning brain tissue. Before such operations, tiny electrodes are inserted into a patient's brain to localize functions like speech and movement, helping the surgeon avoid damaging crucial areas. Information gathered by these electrodes also could answer questions about where perceptual abilities like facial recognition might be located.

While Dr. Etcoff's work is basic research, aimed primarily at discovering how the emotional-signaling processes work, she sees several possible patient applications. Better understanding could help in the treatment and rehabilitation of patients who lose these abilities after brain injury. Earlier recognition of such deficits — which are often difficult to diagnose — could spare months or even years of confusion and distress for patients and their loved ones.

Another topic that Dr. Etcoff studies is facial attractiveness: What characteristics make a face attractive and whether the same qualities are seen as attractive across cultures. Previous research indicated that a composite face, created by averaging features of a large number of people, was regarded as more attractive than any of the individuals that made up the composite.

A recent study from Scotland, however, constructed two types of composites: one from a variety of women's faces and another from only those faces originally regarded as more attractive. Not only was the attractive composite face preferred by both men and women, but a third composite, created by exaggerating the differences between the attractive composite and the average composite, was regarded as the most attractive of all.

Dr. Etcoff, who wrote a commentary that appeared along with the Scottish study in *Nature*, explains that attractiveness seems to be more than averageness. There are specific features in women — large eyes, full lips, narrow jaw, and relatively smaller lower face — that are broadly regarded as attractive. From an evolutionary standpoint, these features could be associated with such reproductive advantages as youth, good health, and fertility.

"I'd like to investigate this area further, broaden it out so we look at male as well as female faces," she says. "And to say these standards are truly universal, we need to study cultures much less exposed to Western ideas of beauty." (The Scottish study used composites of both European and Japanese faces.)

"It will be particularly interesting to look at whether the beauty industry — a multibillion-dollar industry — is imposing cultural ideas about beauty on people or is exploiting our innate preferences," she adds. "My suspicion is that, even across cultures, people find the same facial features more attractive."

Dr. Etcoff cautions that any results of this research have to be kept in perspective. "We have to remember these are just photographs of faces. In real life, there are many other things that go into what we find compelling and appealing in another person." ■

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MGH News

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# Helping traumatized children find a safe place

A young boy is found in a filthy room, emaciated and covered with bruises. Two children watch their father repeatedly beat their mother. A girl is sexually abused for years by a member of her family.

The stories are horrific and all too common today. Those that come to public attention spark outrage against the perpetrators of such abuse and against systems that have not intervened soon enough. Court trials may be played out in the media spotlight, or decisions affecting the futures of children caught in such tragedies may be made behind closed doors.

But after the trials are over, after the visible wounds heal and the immediate danger of harm is gone, there is still much to be done. The emotional wounds inflicted by traumatic experiences rarely heal by themselves and if not attended to can haunt children throughout their lives.

Psychological treatment and support of anyone exposed to extreme violence or other overwhelming experiences is the specialty of the Trauma Clinic, a division of the MGH Department of Psychiatry. The clinic serves patients of all ages and is a valuable local resource for treating children who have been victims of severe emotional trauma.

"Children who are victims of family abuse, or who regularly witness the abuse of a family member, have no source of safety," says Bessel A. van der Kolk, MD, director of the Trauma Clinic. "There is no one to whom they can turn for protection and no way to escape their intolerable situation."

Dr. van der Kolk explains that traumatic experiences not only become embedded in memory but also produce physical changes in how the body responds to stress and emotion. Normal reactions become exaggerated. People react to the stresses of daily life as though they were reliving their trauma: They are overly vigilant, fearful, and unable to trust those around them.

For young children whose physical and emotional systems are immature, the reaction is even more extreme. "Very young children don't understand what is happening to them and tend to react physically to these experiences," Dr. van

*(Continued on Page 2)*

# *Obstetrics program begins offering prenatal care*

For more than 40 years, women who were MGH patients have had to go elsewhere if they were having a baby. But as of July 5, the MGH/Vincent Obstetrics and Gynecology Service now offers prenatal care, marking a significant step in the creation of a comprehensive obstetrics program at the hospital. The process will be completed this fall when labor and delivery facilities open in the new Blake Building.

"An essential ingredient of our progress is the outstanding quality of the team we have assembled and the wonderful collaboration among all the involved departments, as well as the community health centers, to build the obstetrics program at the MGH," says Isaac Schiff, MD, chief of the MGH/Vincent Obstetrics and Gynecology Service.

A special phone line has been set up to provide information and make appointments for women who would like to have their babies at the MGH (*see box on Page 7*). Pregnant women whose last menstrual period occurred after May 31 are able to register now for prenatal care at the hospital.

Fredric D. Frigoletto, Jr., MD, chief of Obstetrics, explains the reason for this cutoff date. "We will not have all the systems in place to deliver a premature baby until Nov. 1. After that date, we can register women at any stage of their pregnancy, but until our delivery facili-

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EDITORIAL

# A leader through changing times

WHEN J. ROBERT Buchanan, MD, became MGH general director in the summer of 1982, this publication noted that among his goals was preserving the hospital's special qualities "in a changing time." No one then could have realized how much the times would change.

Over the past 12 years, regulations controlling how hospitals are paid for patient care changed completely – several times. A new form of health care delivery – managed care – has come to dominate the scene. Today, the need to control health costs while providing top-notch care is stronger than ever, and questions of how health care will be provided and paid for dominate the national political agenda.

Change has also rocked the scientific and medical fronts. AIDS has gone from a medical curiosity to a worldwide health crisis. Social issues such as homelessness, drug abuse, and family violence challenge physicians, nurses, and hospitals alike. Operations like organ transplants, experimental a dozen years ago, are now accepted medical practice. Researchers are unravelling ever-more complex secrets of human genetics and its effect on health problems like cancer.

Dr. Buchanan's guidance and leadership helped the MGH remain strong amid enormous change. The most visible legacy of his tenure is physical: the almost complete renewal of the hospital's Boston campus and the development of its world-class research facility in Charlestown. He also helped attract a new generation of international medical leaders to the MGH. And he was instrumental in creating Partners HealthCare System, Inc., which has put the MGH and Brigham and Women's Hospital in a powerful position to create a model health network for the future.

Dr. Buchanan and his management team faced unprecedented, challenges, and the decisions made were often difficult ones. "Dr. B" could always be relied on for direct and candid answers to the most pointed questions at top-level management conferences, gatherings of the medical and research staffs, or employee town meetings. He has chosen to enter retirement with little fanfare, but his impact cannot be diminished. He has not only preserved but enhanced those special qualities that make the MGH the unique resource that it is. ■

## — A safe place

*(Continued from Page 1)*

der Kolk says. "They may become very aggressive or develop conduct or attention disorders — they can't sit still, they can't focus their minds on a task. Boys particularly tend to be very hyper, while girls are often emotionally frozen — sullen, shy, and antisocial."

### *Loss of social supports*

One result of these reactions is that when abused children reach school age, they find it difficult or impossible to form friendships with other children. "This inability to develop mutually satisfying relationships just makes things worse," Dr. van der Kolk explains. "Having good friends gives you something to fall back on when things aren't good at home. The children who are traumatized in the first years of life miss out on this important source of support."

Typical reactions to trauma can vary with specific experiences. Children who repeatedly witness abuse of a loved one may feel a responsibility to protect the victim or distract the abuser. They may blame themselves for their helplessness and turn their hatred of the abuser inward.

Children who are abused sexually may also blame themselves, sometimes echoing the words of their abuser. Dr. van der Kolk explains that frequently they flee their situation by just tuning it out — retreating into a world of their

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own, imagining that their experience is happening to someone else. Occasionally memories of such abuse are completely repressed or, in the most extreme examples, walled off in multiple personalities.

Some children living in violent neighborhoods may choose an "if you can't beat them, join them" response, allying themselves with gang members or others who threaten them. All of these reactions have in common a search for protection, an effort to create the safe place they cannot find in their home or community.

### *The search for safety*

Therapeutic approaches to helping traumatized children focus on ways to create a "safe place." And the first task is helping children feel safe in their own bodies.

"Part of the reason traumatized kids are prone to take drugs is their bodies are so disorganized. Their nervous systems are out of control, and they take drugs in an effort to calm themselves down," Dr. van der Kolk says. "We teach them relaxation techniques and get them involved in physical exercise, sports, and programs like martial arts or Outward Bound to help them gain a sense of mastery over their bodies."

*Dr. Bessel A. van der Kolk*

*"The traumatized child has only feelings, no words, to deal with life's challenges."*

Appropriate medications also can help restore order to the traumatized child's thinking. Antidepressants like Prozac and medications used to treat attention deficit disorder have proved helpful, as have agents that quiet the body's alarm systems — the physiologic reactions that make up the "fight or flight" response. But Dr. van der Kolk explains that there are more questions than answers in this area.

"These kids have such complicated biologies, we really don't know what medications are best for them. That's a question we need to investigate further."

### *Talking it out*

Only when children have gained some sense of safety can they proceed to the next step: talking about their experiences and trying to make sense of them. "The traumatized child has only feelings, no words, to deal with life's challenges," says Dr. van der Kolk.

"For example, if two 8-year-olds are faced with frustration, the traumatized child will react only with anger — crying, screaming, or using obscenities. Nontraumatized children are able to talk about the situation, say how it makes them feel, and possibly form a plan to solve the problem."

Various standard and specialized psychotherapies are used to help children learn to verbalize in a supportive, nonjudgmental surrounding. Play therapy and artwork allow them to explore their emotions and describe them in indirect, less threatening ways.

Those involved in caring for the children also participate to gain understanding of the child's needs, to learn how to deal with disruptive behavior, and often to address their own stresses and traumas. "You might have a mother who's dealing both with the traumatized child and her abusive boyfriend. Or the child could be cared for by grandparents who are also coping with the loss of the child's parent — their own son or daughter. They need help to provide the supportive environment that is essential to the child's recovery," Dr. van der Kolk says.

The final step is helping children learn to make those essential personal connections with their peers. "That is really the most important thing," says Dr. van der Kolk, "to learn that, although life is scary, you can form alliances with others that are mutually beneficial. You don't need to approach every relationship like you're going to be victimized or you're going to victimize somebody else."

### *A vicious cycle*

If traumatized children do not receive the help they need, their outlook can be grim. Many of them try to cope with their feelings by repeating the abuse they experienced on others. "One of the theories of why abused children become abusers is a process called identification with the aggressor," Dr. van der Kolk says. "They think that if they act like the person who hurt them, they will become powerful. It's really a way to deny that anything terrible happened to them or could happen again."

Similarly, traumatized children may seek a perverted source of self-identity and self-esteem in criminal gangs. Alcohol and drugs are ways to block painful memories and suppress uncontrollable emotions. Bizarre behaviors like self-mutilation are almost always related to childhood trauma, says Dr. van der Kolk.

Some traumatized children do seem to rise above their painful beginnings without assistance. Many rely on their intelligence, aptitudes, or talents in art, sports, and music to find a means of escape.

Dr. van der Kolk explains: "These are the people who have been able to wall their trauma off from their lives and concentrate on an area where they can excel. They may become very successful in their work, but if they never deal with their experience, they find it impossible to build loving, intimate relationships."

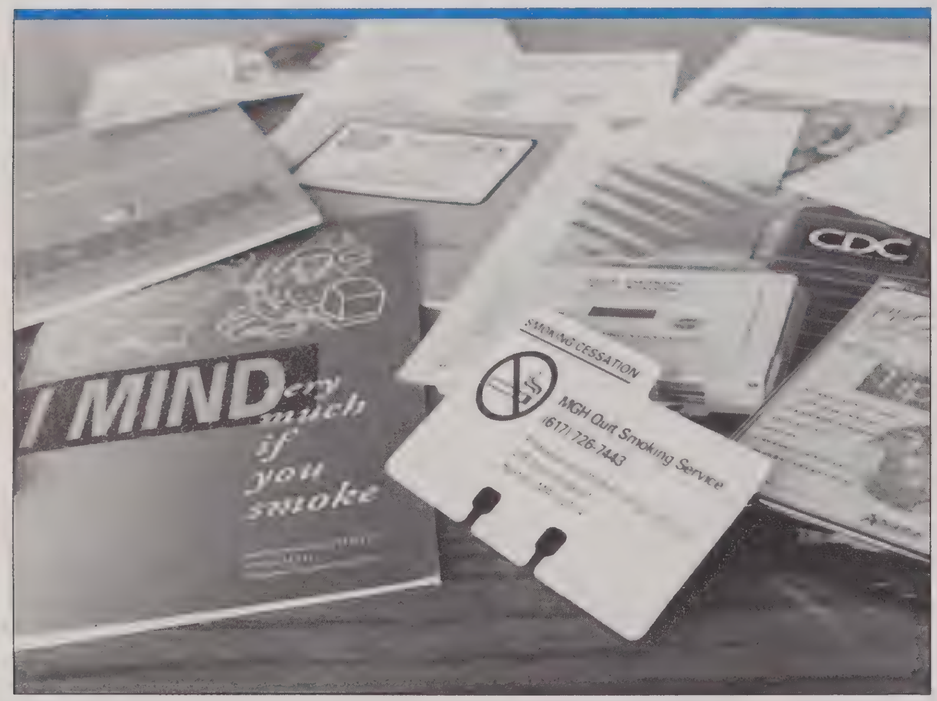
The work with children done by the Trauma Clinic staff — which includes psychiatrists, psychologists, and social workers affiliated with the MGH, Harvard Medical School and the North Suffolk Mental Health Association — can be lengthy, grueling, and frustrating. But the results can be worth it.

"People are remarkably resilient," Dr. van der Kolk says. "If you can provide a supportive environment and help these kids feel understood, if you can help them verbalize their feelings and make sense out of what has happened to them, you really can get through to them. I keep being impressed with how successful we are." ■

# Strategies for staying smoke-free

IT HAS NEVER been easy to quit smoking. Although scientific evidence of nicotine's addictive nature is relatively recent, smokers spoke of being "hooked" long before tobacco's harmful effects were recognized. As social acceptance of smoking wanes, smokers often feel trapped between increasing restrictions regarding where and when they can smoke and a perceived inability to stop what most of them recognize as a hazardous habit.

But there is some good news. Health professionals have learned much about how smokers can successfully quit and what techniques are most useful. New research may help design more programs that can meet the different needs of individuals and lessen the risk of relapse.



*Informational materials, relaxation tapes, nicotine replacement, and support programs like the MGH Quit Smoking Service can help in the struggle to become smoke-free.*

### *Learning from mistakes*

"Quitting smoking is a process," says Nancy Rigotti, MD, an internist and director of the MGH Quit Smoking Service. "You might try once, stay off cigarettes for a while, and then make a mistake and start smoking again. But if you can learn from that mistake, if you can understand the circumstances that led you to pick up that first cigarette, maybe next time you will quit for good."

Dr. Rigotti explains that the average ex-smoker tried three times before successfully quitting. She notes that stopping involves winning several battles.

"First, people have to break the addiction to nicotine, which is a psychoactive drug that produces real withdrawal symptoms," she says. "Then they have to break all those habit patterns they have developed over their lives — having a cigarette after meals or with their morning cup of coffee. "In addition, some smokers use cigarettes as a way to cope with negative emotions like anger and frustration or to directly regulate their moods."

### *Setting the groundwork*

There are people who are able to quit on their own. For many, however, support or counseling can mean the difference between staying off cigarettes and starting to smoke again. Laying the groundwork for a successful effort takes several months or longer, and various stages are involved in mentally preparing to quit.

Smokers may start out not even thinking about quitting, Dr. Rigotti says. Then they begin to consider the drawbacks of smoking and the advantages of stopping. They pay more attention to health information and may start to worry about their smoking's effect on their children or other loved ones.

The next stage is a period of preparation to quit. This could involve looking into programs, cutting back on how many cigarettes are smoked, and setting a quit date. It is a time to develop mental focus and energy before reaching the actual point of putting out that last cigarette.

Making the decision to quit, Dr. Rigotti adds, is something smokers have to do for themselves, not in response to pressure from a friend or family member. "Those who quit for other people don't stay off cigarettes very well because they can always find an excuse to smoke. Especially if they become angry with the other person, smoking is a perfect way to get back at them."

### *Quitting strategies*

Today's state-of-the-art strategies for helping smokers quit have two main components: nicotine replacement and behavior modification. For some, behavior modification alone may offer the support needed to break the habit.

"Behavior modification means becoming more aware of the triggers that make you smoke and then starting to break the link between those triggers and picking up a cigarette," Dr. Rigotti says. "It's very simple, but it takes a lot of practice."

One of the ways to break that link is a technique called urge stopping, explains Thelma Tisdale, RN, MPH, program coordinator for the Quit Smoking Service. "We ask people, when the urge to smoke strikes, to say to themselves — out loud if possible — 'Stop, wait, I'm learning to be a non-smoker.'

"The next step is to think about their reasons for quitting and, once they've interrupted that urge, to do something else: Get a glass of water, go for a walk, call a support person, or take a shower. People don't believe it will work, but incorporating another activity can really stop the automatic process of lighting that cigarette."

Other aspects of behavior modification include relaxation exercises to cope with the stresses relieved by smoking. Finding positive ways to reward oneself for the successes along the way is an important factor, and personal support from a counselor, group members, or an ex-smoking "buddy" can help one get past the rough spots. Another key aspect is anticipating those times when cigarettes may be particularly tempting and planning a strategy for resisting that temptation.

"It's a very bad idea for people to drink alcohol while they're trying to quit smoking because alcohol lowers their resolve," Dr. Rigotti notes. "That doesn't mean they

## Call to quit

The MGH Quit Smoking Service offers a wide variety of multidisciplinary programs to help smokers reach their goal of becoming nonsmokers — permanently. Ranging from group programs to in-depth individual counseling, the service features behavioral modification, stress management, exercise and diet advice, and nicotine replacement prescriptions.

Special emphasis is placed on the problems of smokers who have failed in previous attempts to quit or who have not yet made the decision to stop smoking. For more information or to schedule an evaluation appointment, call the Quit Smoking Service at (617) 726-7443.

have to stop drinking permanently, but during those first few months it's smart to stay away from anything that could make it easier to start smoking again."

When behavior modification isn't enough, nicotine replacement may be required. When properly used, the nicotine patch or nicotine gum — both of which require a doctor's prescription — can eliminate nicotine withdrawal symptoms while one is learning new, smoke-free habits. While early reports on the effectiveness of nicotine replacement were inconclusive, more recent studies indicate that it can double the chance of a successful quit effort.

"When people have tried behavior modification and nicotine replacement and still are unable to quit, we then screen them for the factors that make quitting particularly difficult — including mood disorders and substance abuse," Dr. Rigotti says. "Such problems must be addressed before people can quit successfully, and these folks may need specialized, more intensive treatment and support."

### *Current research*

Better ways to help those who want to quit smoking may come from research. One of the areas of greatest interest, Dr. Rigotti explains, is the link between smoking and mood disorders.

"We know that smokers who suffer from depression are often unsuccessful at quitting, unless their depression is treated first. In addition, there are people who develop symptoms of depression or anxiety for the first time after they quit," she says. "Understanding why and how this could happen might help us identify those who are at risk and make us better able to devise preventive strategies."

Another subject to investigate is the link between illness and the motivation to stop smoking. "We know that one of the most effective incentives to quit smoking is to have your first heart attack," Dr. Rigotti says. "About one-third of these people stop smoking on their own. They're frightened, the knowledge that smoking is bad for people suddenly becomes personalized: 'Smoking is bad for me!' And they have to spend a week or so in a place where they can't smoke."

To examine how the experience of hospitalization might help patients quit smoking, the Quit Smoking Service has started a research project led by Dr. Rigotti. Inpatients admitted to either the medical or surgical services will be offered the opportunity to participate, and those choosing to do so will be randomly divided into two groups. One will receive usual hospital care, the other will have a brief bedside smoking counseling session with Quit Smoking Service staff, supplemented by written materials and telephone followup after discharge.

"We want to see whether the counseling can increase the number of people who quit smoking after a hospital stay," Dr. Rigotti says. "It would also be interesting to see if those with smoking-associated problems have more success quitting."

No one expects that the process of quitting smoking will ever be easy, but these and other research projects may someday help health care professionals know which techniques will work best for particular patients.

Dr. Rigotti stresses that no matter how many unsuccessful attempts have been made, it is never too late to try again. "Quitting smoking is a learning experience; it's not a test of will power. If you've been able to stop before and stay off for a while, you're already on your way. It's important to keep trying." ■

## *MGH and BWH refuse tobacco research funds*

In May both the MGH and its Partners HealthCare System affiliate Brigham and Women's Hospital (BWH) announced that they would no longer accept new research support from two tobacco-industry-supported foundations: the Council for Tobacco Research — USA, Inc. (CTR) and the Smokeless Tobacco Research Council (STRC). The decision was initiated by several MGH researchers who were worried that research sponsored by these organizations was being used to bolster the tobacco industry's claims that links between tobacco and disease remain unproven.

"We were concerned that the tobacco industry had been using the very existence of its research funding through the CTR to imply that doubt still remained," says Ronald S. Newbower, PhD, MGH corporate vice president for Research and Technology. "The MGH research leadership and Board of Trustees took this stand to reinforce our emphasis on health and well-being and to ensure that we did not lend credibility to the public relations efforts of the tobacco industry."

In 1993, the MGH appointed a diverse group of researchers, including several current or former recipients of support from the foundations, to examine the policy of accepting funds from the CTR and STRC. While a broad array of issues were discussed — including academic freedom of researchers and any potential health benefits that could result from CTR-supported research (neither hospital had received funds from STRC) — those involved in reviewing the issue determined that any perceived support for the tobacco industry ran counter to the hospital's mission of health promotion and preservation.

The MGH and BWH are the first hospitals in the Boston area to adopt a policy refusing tobacco industry funding for research. ■

# Why obstetrics returns to MGH

One of the most frequently asked questions since the formation of Partners HealthCare System, Inc., has been whether the MGH would proceed with its plans to open an obstetrics program. Many people wondered whether the new relationship with Brigham and Women's Hospital (BWH), which has the largest such service in New England, would make an MGH program unnecessary. But the reasons behind the MGH's original decision to reintroduce obstetrics have not changed.

Simply stated, the MGH is providing a much-desired service to a group of patients who already look upon the MGH as "their hospital." These include patients of our Charlestown, Chelsea, and Revere community health centers; women who are long-time MGH patients because of chronic health problems like diabetes and heart disease; and MGH employees and their families. All of these women — even those who took advantage of the hospital's fertility or genetic counseling services — previously had to be referred to obstetricians elsewhere when they became pregnant.

With the return of obstetrics, the MGH becomes a true full-service hospital. MGH patients who become pregnant are now able to have their babies within a familiar system, under the care of familiar physicians, without the previous fragmentation of care.

The affiliation with BWH allows the two obstetrics programs to work together — sharing information, developing teaching and research activities, and working to keep costs under control. It has been frequently noted that the two hospitals serve patients from different regions — the MGH from downtown Boston, adjacent communities, and the near northern suburbs; BWH from southern and western Boston and communities to the south and west. The complementarity that makes the two hospitals such ideal partners also supports offering obstetrics at both locations as part of an integrated system centered on community-based primary care. ■

## — Prenatal care

(*Continued from Page 1*)

ties are ready, we have to follow these guidelines."

Sherrin Langeler, RN, CNM, director of midwifery, adds: "We don't want to have to send one of our patients somewhere else if she goes into premature labor. That is the opposite of our program's philosophy, which stresses continuity of care for all patients — mothers and babies."

Eligible patients who call the information line will receive a comprehensive initial telephone screening, including discussion of such issues as past pregnancies, underlying health conditions, and whether they prefer to receive care from an obstetrician or a nurse midwife. Gathering all appropriate information in advance will help the first prenatal care visit go smoothly.

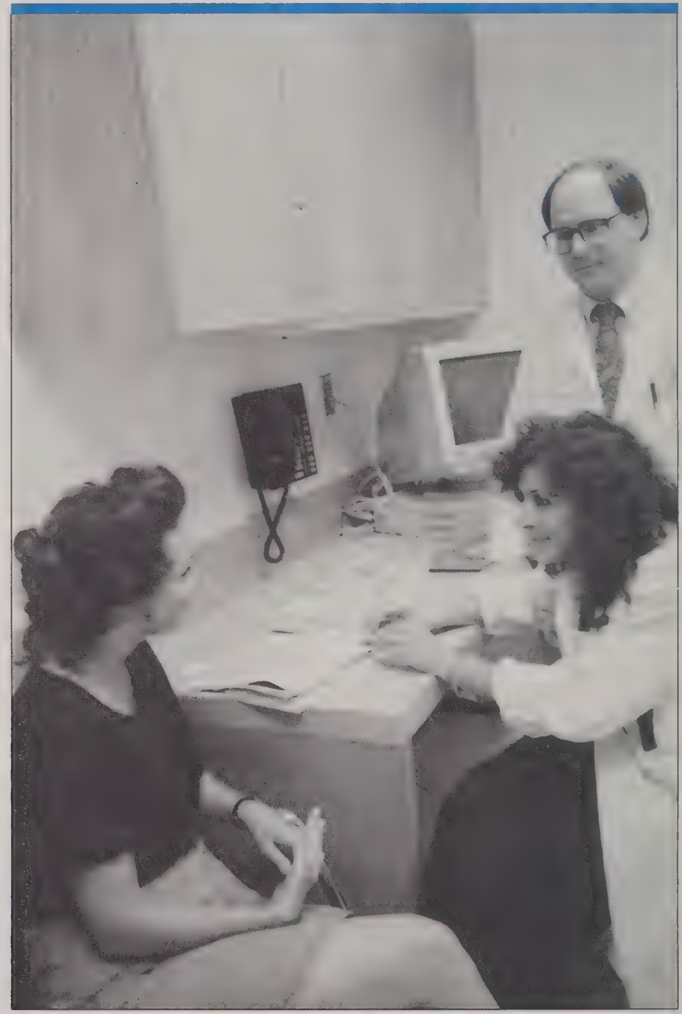
Women inquiring about the MGH program who do not fit the screening guidelines will be referred to other obstetrics programs in the area, including the program at Brigham and Women's Hospital. "The new Partners HealthCare System relationship with the Brigham will be particularly helpful during this period of change," Dr. Frigoletto says.

For patients of the MGH-affiliated community health centers, where ambulatory obstetrics care has always been available, a transition plan has been developed. Expectant mothers who already have a relationship with an obstetrician or midwife are able to stay with their provider and deliver their babies as planned. Anyone preferring to have her baby at the MGH, however, can transfer to the hospital's program if she will not be more than 22 weeks pregnant by Nov. 1. By March of next year, the MGH obstetrics staff will provide all pregnancy-related services for the health centers.

On the main campus, ambulatory offices for the obstetrics program are currently located on the ground floor of the Wang Ambulatory Care Center, convenient to such support services as patient registration, blood testing labs, and ultrasound. This fall all main campus patient services of what will be called the MGH Mother & Child Center will move into the Blake Building.

"For our outpatients, we'll offer one-stop shopping," Ms. Langeler says. "Everyone involved will be on the same floor, including dietitians, social workers, ultrasound specialists, genetic counselors, obstetricians, and nurse midwives."

Midwives, Ms. Langeler explains, are trained to care for women during normal pregnancies and deliver their babies. "We're also trained to recognize possible complications and consult with physicians, when appropriate," she adds.



*Hiyam Dupont, RN (seated, right), and Dr. Robert Blatman discuss prenatal care guidelines with expectant mother Caren Farber.*

## Call 724-BABY

Women who have recently become pregnant and would like to have their babies at the MGH can call **(617) 724-BABY** (724-2229) to register for prenatal care. Physicians who would like to refer an obstetrics patient to the MGH program or to consult with MGH staff members about an expectant mother's care should call a separate number — (617) 724-3358.

“Sometimes we co-manage those patients with the physician, but if a serious complication arises, we transfer them to an obstetrician's care.”

Dr. Frigoletto stresses the cooperative aspect of the relationship between physicians and midwives in the MGH program. “We believe in a seamless partnership between obstetrics and midwifery. If a patient develops a minor medical problem, there's no reason that she should leave her midwife. We want to provide the kind of care she chooses.”

Hiyam M. Dupont, RN, BSN, chief nurse of Ambulatory Obstetrics, says that the principle of continuity extends throughout the prenatal care period. “Because we're a group practice, some patients wonder whether they'll be seen by the same providers on each visit. They will. The only time that would differ is during labor, when the on-call midwife or obstetrician — both are always available — would manage the labor and perform the delivery,” she says.

One feature that will help integrate the hospital-based obstetrics program with the health center services will be a new, electronic medical record-keeping system. Michael F. Greene, MD, director of Maternal-Fetal Medicine, explains that information and test results for each patient can be entered into computer terminals where they will be instantly available to those involved in her care.

“People won't have to carry paper reports back and forth and worry whether the information they have on a patient is current. We hope that it will make everyone's work a lot easier and make patient care better and more efficient,” Dr. Greene says.

The MGH program also emphasizes patient and family education, including special classes to help children prepare for the arrival of a new sibling. Plans are under way to develop a system for a health care professional to visit new mothers at home, if they wish, and provide additional education and support.

“Everyone here is dedicated to helping each patient have the most natural pregnancy and delivery possible, with full consideration of her preferences and sensitivity to issues like ease of access and cultural diversity,” Dr. Frigoletto says. “With the support we've received throughout the hospital and with the outstanding advanced services of the MGH available for any unexpected problems, we think our program will be second to none.” ■

# *Rare operation avoids amputation*

When John Lee, MD, of Winchester broke his leg in what he now describes as a “fortuitous fall,” doctors discovered cancer in his thigh bone. The 61-year-old chief of Medicine at a local Massachusetts hospital faced two unappealing options: have his leg amputated at the hip or have his femur (thigh bone) permanently replaced with a metal rod, a course of action notorious for failure. A third option offered more hope — go to Henry J. Mankin, MD, chief of Orthopædics at the MGH.

Well known for performing surgical bone allografts, in which donated cadaver bones are used to replace bone destroyed by disease or trauma, Dr. Mankin helped build the MGH's international reputation in this field of surgery. To date there have been 840 allograft operations at the MGH.

But the surgery Dr. Lee required to save his leg, a total femoral allograft, is rare even by MGH standards: It has been done only nine times here, even though the MGH is one of the few hospitals in the United States offering this surgical option.

The complexity of total femoral allograft surgery requires two surgical teams to work concurrently. While one team operates on the patient to remove the destroyed femur, a second team prepares and attaches metallic knee and hip joint replacements to the cadaver bone.

“This operation is more hazardous than partial allograft surgery. It is more of a challenge,” says Dr. Mankin. “You must find the right sized cadaver bone and fit it into the patient's existing soft tissue envelope. You are exposing blood vessels and nerves along the whole thigh, and there is a lot of blood loss. There is the risk of infection and, after surgery, a concern of fracture and rehabilitation for two joints.”

Bones for allograft surgeries are procured from the MGH Bone Bank, which Dr. Mankin established in 1971 when he launched the allograft program at the MGH. While many hospitals have small

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*Dr. Henry Mankin (left) and his surgical team prepare a patient for a total femoral allograft, complete replacement of the thigh bone.*

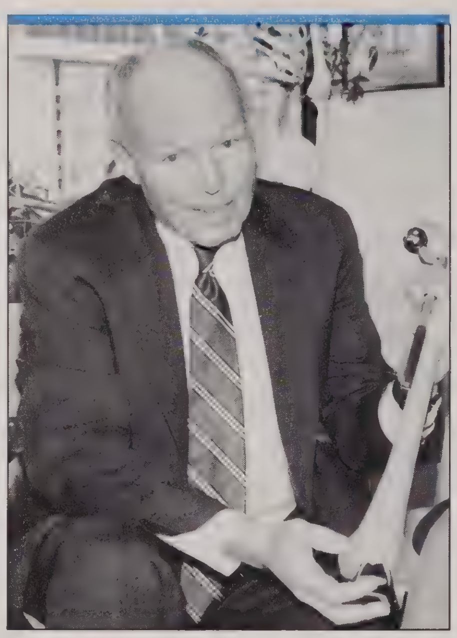
(Continued from Page 7)

inventories of bones, the MGH's program is unusually large and varied, with between 200 and 300 available bones at any given time. Bones are preserved from both surgical patients and cadavers and then frozen. Because the bone tissue is dead, it does not have any blood or viable marrow remaining. This makes the risk of rejection, which is often high in transplant surgeries, very low in bone allograft procedures.

Ann-Marie Starck, PT, physical therapist, has treated five total femoral allograft patients. She says the rehabilitation process can be divided into two phases. Immediately after surgery, physical therapists work with patients on basic functions like learning to walk, often on two crutches with a somewhat cumbersome brace. As the patient makes progress, rehabilitation focuses on joint mobility, increasing strength and stability of the muscles around the hip and knee, and developing a good walking pattern.

In what might seem to be an odds-defying coincidence for such a rare surgery, two additional total femoral allografts were performed at the MGH within a matter of weeks this past spring. For 61-year-old Charles Dunn of New York, a series of operations following complications from a hip joint replacement had led to significant bone deficiencies. Eventually he fell and fractured his leg so seriously that it was beyond reconstruction.

> *"Mr. Dunn has been through terrible problems. By the time I saw him he had only three inches of femur remaining."*



*Dr. Hugh Chandler shows how metallic joint replacements are attached to the donated femur before implantation.*

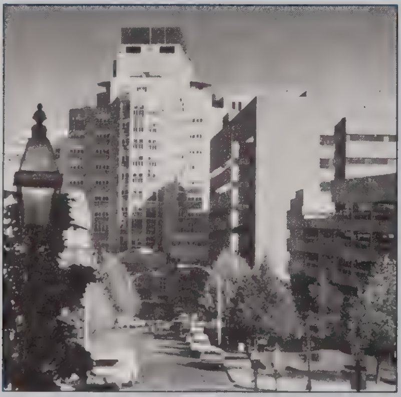
"I remember when they told me, in front of my daughter, that I could lose my right leg," says Mr. Dunn. "My doctors in New York said they were just not equipped to help me." They suggested he come to the MGH.

According to Hugh Chandler, MD, MGH orthopædic surgeon: "Mr. Dunn has been through terrible problems. By the time I saw him he had only three inches of femur remaining between the bone loss from his previous operations and damage from the fracture. That is not enough for a reconstruction, so we performed a total femoral allograft."

Mr. Dunn now says, despite a little soreness in his leg, overall he is feeling great. "I think Dr. Chandler is wonderful, and the MGH is the best hospital."

Also this past spring, a 77-year-old woman came to see Dr. Chandler after a cemented hip replacement became infected. After the infected and damaged area was cleaned up, only a remnant of her femur remained. She too successfully underwent total femoral allograft surgery. Dr. Lee's successful bone allograft surgery took place in March. Within a few months of their surgeries, all three patients were walking.

"Allograft patients do quite well, though there are not any professional athletes in the group," says Dr. Mankin. "I think that having some diminished function is probably all right with them, considering they all faced losing a leg." ■



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MGH
News

Massachusetts General Hospital, Boston, Massachusetts

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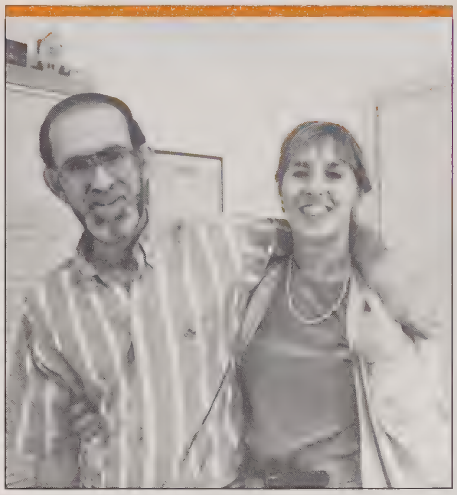
# Operation restores mobility to Parkinson's patient

ONLY last year, at the age of 47, Richard Weeden was trapped in a body that could hardly function. Fourteen years earlier, he had been diagnosed with Parkinson's disease, a condition affecting areas of the brain that control movement.

For some time, his symptoms of trembling hands, rigid muscles and slowness of motion had been controlled by medication. But in 1989, he began to experience a common side effect of the drugs, uncontrollable movements called dyskinesias. When he walked, his legs would jerk up and forward, in a bizarre parody of a military goose step, making it impossible to walk in a straight line. Even at rest, his legs constantly writhed and twisted.

Without the medication, Weeden was practically frozen. His hands trembled constantly, and any attempt to move was excruciatingly slow. His balance was so poor that he risked falling whenever he tried to walk. Sometimes he had to move around his home on his hands and knees. Finally, he could not even get out of bed. His wife Betty, a registered nurse, thought she would have to hire an attendant to stay with him during the day while she worked.

"Before Rick got Parkinson's, he was very physically active," she says. "We waterskied, we sailed; he loved to do carpentry work around the house. Then slowly, inexorably, he lost everything."



*Richard and Betty Weeden*

John Growdon, MD, the MGH neurologist who oversaw Weeden's care, says: "We were very frustrated with all our efforts to help him with medication. He had only a few minutes every day when he could function at all."

Today, Weeden's situation has profoundly changed. He walks more than five miles a day. He is able to care for himself and work around the house. While he is not free of Parkinson's symptoms, he is once again an active participant in the lives of his family and friends.

### *Revival of an obsolete operation*

This transformation is the result of an operation performed at the MGH, an operation that resulted from a collaboration between an MGH neurosurgeon and a Finnish surgeon who is leading the revival of a procedure thought obsolete decades ago.

The operation, called a pallidotomy, was one of several used during the 1950s and '60s to treat Parkinson's. All these

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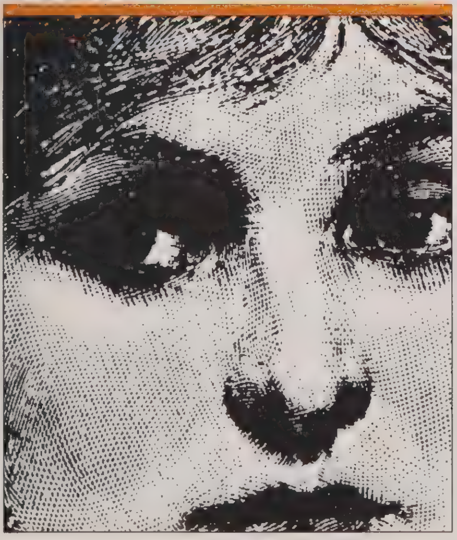
# *Ovarian cancer: putting the worry into perspective*



THE RECENT DEATH of actress Jessica Tandy may again draw public attention to the disease that took her life after a four-year battle: ovarian cancer. At a time when many women are taking positive steps to protect themselves against cancer, recommendations regarding ovarian cancer may seem frustratingly incomplete. One of the most recently published studies concluded that current methods for finding early ovarian cancer do not work very well.

In the light of such news and Tandy's death, growing concern among woman about this disease is understandable. Ovarian cancer is the fourth leading cancer killer of women, and more than 60 percent of women diagnosed do not survive for five years. But for most women, excessive worry about ovarian cancer is misplaced because they are at relatively low risk of developing it. Consulting with a doctor about their personal risk and the factors that can affect it is the best strategy for all concerned women.

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procedures involved making small lesions (areas of damaged tissue) in parts of the brain involved with motion control. In the pallidotomy, the lesion is placed in an area called the globus pallidus. Through a process that is still not well understood, the operation successfully relieves symptoms for many patients *(see sidebar)*. When medications that produced similar effects without surgery became available in the late '60s, the pallidotomy was abandoned.

Neither drugs nor operations can cure Parkinson's. Eventually patients need higher doses of medication to control their symptoms. Like Richard Weeden, many develop drug-induced dyskinesias and find themselves existing on a precarious edge: motionless without medication, moving uncontrollably with medication.

For the most severely affected patients, surgeons have continued to offer another operation called a thalamotomy. But while that procedure does control tremor and muscle rigidity, it can cause the third major symptom, slowness of movement, to get worse.

Because of this limitation of the thalamotomy, Lauri Laitinen, MD, PhD, a Finnish neurosurgeon working in Sweden, began once more doing pallidotomies in patients with the most severe symptoms. In 1992, he published results showing dramatic results for most patients, sparking interest among many neurosurgeons, including G. Rees Cosgrove, MD, who was about to join the MGH staff.

### *A series of frustrations*

News about Laitinen's success also spread through support and information networks set up by Parkinson's patients and their families. The Weedens heard about the operation and traveled for an evaluation from their home in Portsmouth, R.I., to a New York teaching hospital that planned to offer the procedure.

A lack of coordination among the staff of the New York center meant that the Weedens had to make several trips to the city and back. When asked to make appointments with several additional doctors, again requiring separate trips, they decided not to return to New York.

Frustrated, the Weedens began to consider traveling to Sweden. At the suggestion of Growdon, they also spoke with Cosgrove, who had joined the MGH staff. While he had experience with the thalomotomy operation, Cosgrove had not yet done any pallidotomies, so he concurred that Weeden's best chance was to seek care from Laitinen.

Weeden was accepted as a patient by Laitinen, and in what was to prove a lucky coincidence, his operation was scheduled at the time when Cosgrove was in Sweden to learn the procedure. Cosgrove observed his treatment and offered to provide follow-up care back in the United States.

Unfortunately, the results of the first operation in June 1993 were disappointing. Weeden experienced some relief from the Parkinson's symptoms, but it lasted only a few days. Laitinen recommended allowing time for his brain to heal from the operation before deciding on a further course of action.

### *Pinpointing the problem*

MRI examinations taken at the MGH several weeks after Weeden's return pointed to a possible explanation of the problem. "From what I'd learned about the ideal placement of the lesion, it looked like the position within the globus pallidus was not quite right," Cosgrove says.

Laitinen agreed with the assessment and accepted an invitation to come to Boston and observe a second procedure earlier this year. The two surgeons independently reviewed detailed preoperative imaging studies, and both agreed on the specific location for the new lesion.

In the operating room, Cosgrove made a tiny hole in the skull and inserted a needle-like probe that carries an electrical current into the brain. The electrode is insulated to allow current to pass out at the tip only. Depending on how much current is applied, the electrode can stimulate, inactivate or destroy the cells it touches. In Weeden's case, the probe was passed into the globus pallidus on the left side of the brain, which affects movement on the right side of the body.

Because no pain-sensing nerves are located inside the brain, patients remain awake during the operation, under local anesthesia. With the help of the patient, the surgeon can further confirm the target for the operation and avoid damaging crucial nearby structures. "We talk to the patients during the procedure and do a number of intraoperative tests," Cosgrove explains. "By passing a small current through the brain, we can see improvement in function right away."

When the electrode is in the right spot, a stronger current is applied that destroys cells in a small area. Weeden recalls the moment: "Dr. Cosgrove was doing the operation, and Dr. Laitinen was asking me to move my right leg to see if the probe was in the right place. They agreed that the position was right, and Dr. Laitinen said to me, 'You're not going to have any trouble with that leg again.' I was skeptical, but since then it has been rock steady. I haven't had any dyskinesia in that leg at all."

> **"Now I take care of the house myself and make the meals. I can get out for a walk every day. To me, that's just wonderful."**
>
> **— Richard Weeden**

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### *Improved mobility, balance*

Weeden's entire right side, which was most seriously affected before the operation, has improved remarkably, and his sense of balance also has returned. Although he still takes medication to control symptoms on the left side and has some dyskinesia in that leg, he and his wife are delighted with his restored mobility.

"There are so many things you take for granted when you're healthy. I couldn't even roll myself over in bed at night, much less get up to go to the bathroom," he says. "Now I take care of the house myself and make the meals. I can get out for a walk every day. To me, that's just wonderful."

The pallidotomy is not a cure for Parkinson's; symptoms can eventually return as the degenerative process that underlies the disease continues. But the operation will most likely give Weeden several additional years of functional mobility. And if symptoms on his left side worsen significantly, the operation can be repeated on the untreated right side of the brain for a few more years of relief.

"Rick's improvement has been like a miracle, and we're so grateful to Dr. Cosgrove, Dr. Laitinen, and everybody at the MGH," Betty Weeden says. "The nurses who cared for Rick were just fantastic. Before this operation I felt like I didn't have my husband any more; I was a nurse taking care of a patient. Now I have my husband back." ■

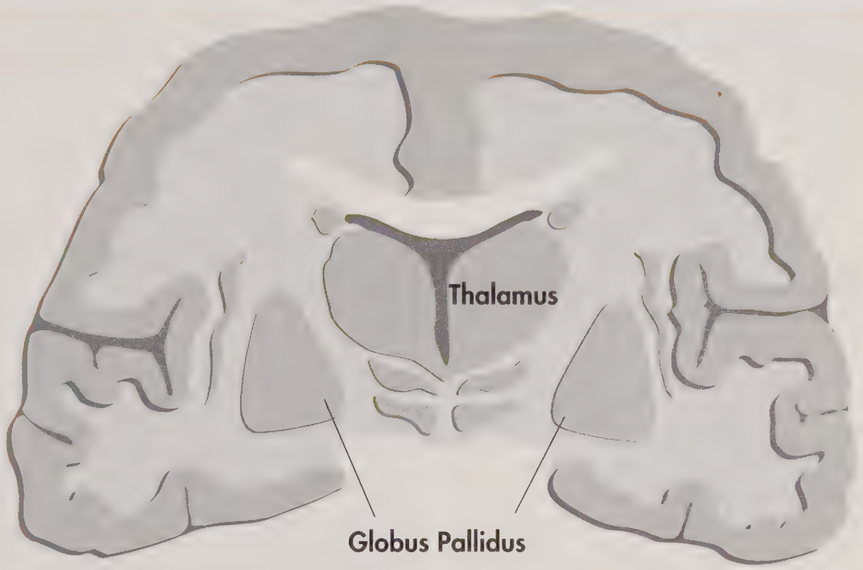
# Trying to restore the balance

PARKINSON'S disease is caused by the death of certain brain cells secreting a chemical called dopamine, one of several neurotransmitters that carry signals between brain cells. Normally, dopamine operates in a delicate balance with other neurotransmitters to help coordinate the millions of nerve and muscle cells involved in movement.

Without enough dopamine, this balance is upset. People begin to exhibit the typical symptoms of Parkinson's disease — a trembling of the hands or head, increasing rigidity of muscles and a slowness of motion. The disease typically appears in older people, with most being diagnosed in their 50s or 60s, and usually continues to worsen throughout life. Some patients, like Richard Weeden, develop symptoms much earlier *(see story, page 1)*.

John Penney, MD, an MGH neurologist, evaluates Parkinson's patients for surgery. He notes that several conditions can produce symptoms of the disease — including infections of the brain, certain drugs and brain injury (as in the case of boxer Muhammad Ali). But the ultimate cause of true Parkinson's disease is still a mystery.

For decades, neurosurgeons tried to relieve the involuntary movements of conditions like Parkinson's by operating on parts of the brain involved with motion control. As more was learned about brain anatomy, attention was directed toward a cluster of deep-brain structures, including the basal ganglia, the thalamus and the globus pallidus. These form a "circuit" that transfers motion-related signals from the brain to the spinal cord and thus to the rest of the body.



*This side-to-side cross section of the brain shows several deep-brain structures involved in control of motion. Both the thalamus and the globus pallidus have been targets for operations designed to control Parkinson's disease symptoms.*

In the late 1940s, introduction of a technique called stereotactic surgery made operating on the brain much safer. Stereotaxis uses a metal frame to hold a patient's head absolutely still during imaging studies and the operation. Measurements can be taken to precisely locate structures within the brain, and delicate instruments inserted through a tiny hole in the skull to remove or destroy tissue.

With less risk of damaging healthy brain tissue, surgeons used stereotactic surgery to control the symptoms of Parkinson's by creating small lesions within these brain structures. While such operations were used to treat advanced Parkinson's symptoms during the 1950s and '60s, they were largely abandoned when drug treatment became available. One of the operations, the thalamotomy, did continue to be offered, and now pallidotomy, creation of a lesion in the globus pallidus, is being revived for selected patients.

"This operation is not for everyone," says John Growdon, MD, MGH neurologist. "Most patients are treated successfully with medication. But each patient is unique, and a few, like Mr. Weeden, develop exaggerated responses to the drugs that can be just as disabling as the illness. Without this operation, there isn't much else we can offer such seriously affected patients."

Why making a lesion in the brain can relieve Parkinson's symptoms is a mystery. Some evidence indicates that part of the globus pallidus is overactive in the disease. The lesion may suppress that area and partially restore the lost balance between neurotransmitter systems. G. Rees Cosgrove, MD, the MGH neurosurgeon who performs pallidotomies, has now done a total of eight operations, seven of them at the MGH, which currently is the only hospital in New England offering the procedure. ■

# —Putting the worry into perspective

*(Continued from Page 1)*

One of the most powerful risk factors for ovarian cancer is family history. For a woman with no family history the risk is about 1 in 70 (around 1.5 percent) that she will develop ovarian cancer during her lifetime. If one of a woman's immediate relatives (mother, sister or daughter) develops ovarian cancer, her risk rises to 1 in 20 (5 percent), and if two such relatives have the disease, the risk is 1 in 15 (7 percent).

Among this highest-risk group is a small subset of women from families with many instances of both ovarian cancer and other malignancies. For them the risk is markedly increased — as high as 50 percent — and the knowledge that a woman belongs to such a family signals the need for especially careful followup. Actress Gilda Radner, who died of ovarian cancer in 1989, was not aware of her family's cancer history until after her tumor was diagnosed at an advanced stage.

### *Choices can affect risk*

Age is also a risk factor for ovarian cancer; most are diagnosed in women over 50. What many women do not realize, however, is that some of the personal choices they make can actually change their risk of ovarian cancer. Anything that interrupts ovulation — the normal monthly release of an egg — has a significant impact on cancer risk.

Arlan Fuller Jr., MD, chief of Gynecologic Oncology at the MGH, leads a comprehensive treatment program for ovarian cancer patients. "Each pregnancy reduces a woman's risk of ovarian cancer by 12 to 14 percent," he says. "Women who don't plan on having many children should know that taking oral contraceptives for 10 years can also reduce the risk of ovarian cancer by as much as 80 percent. We hear a lot about possible negative effects of birth control pills, but there are also real benefits."

Recent evidence indicates that tubal ligation also may reduce ovarian cancer risk, although this procedure is not recommended solely as a cancer preventive. "One theory is that many ovarian cancers are caused by environmental carcinogens, like talc, making their way up through the reproductive tract and getting trapped in cysts that commonly develop when women ovulate," Fuller says. "The observation that tubal ligation reduces risk fits logically into that hypothesis, because it cuts off the connection between the ovaries and the outside world."

### *Imperfect defensive strategies*

Putting individual risk into perspective can help a woman and her doctor decide which of the available strategies to detect ovarian cancers, however imperfect, is right for her. Annual pelvic exams, recommended for every adult woman, are a first line of defense, but the limitations of such exams in finding ovarian cancers recently sparked interest in further screening with ultrasound or a blood test called CA 125.

Karen Carlson, MD, director of the MGH Women's Health Associates, has been investigating the effectiveness of ovarian cancer screening for several years. In a report published this summer in *Annals of Internal Medicine,* she and two colleagues from the MGH General Internal Medicine Unit — Steven Skates, PhD, a biostatistician, and Daniel Singer, MD, director of Clinical Epidemiology — reviewed available information about ovarian cancer risks and calculated possible benefits of screening with ultrasound and CA 125. They concluded that screening could not be recommended for women who had no family history of ovarian cancer. Women with a family history should discuss other risk factors with their physicians before deciding on screening tests, and those who belong to high-risk cancer families should be carefully followed by ovarian cancer specialists.

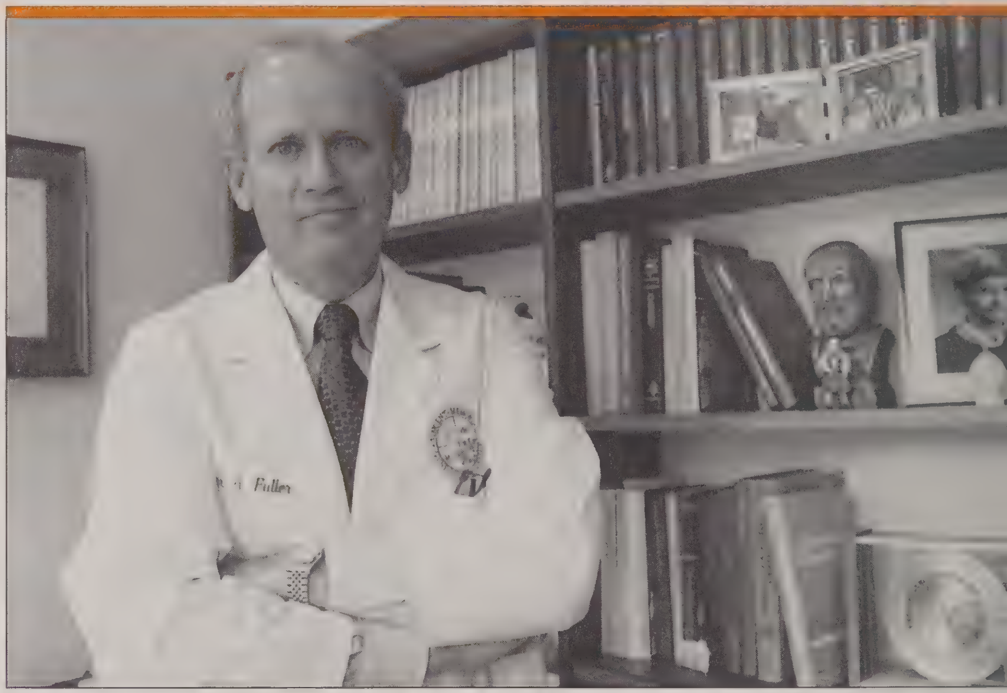
Carlson explains: "Human nature being what it is, there were a lot of requests after Gilda Radner's death for ovarian cancer screening tests. Unfortunately, the science really isn't where it needs to be for screening to make sense for most women."

### *Positive problems*

The problem with the available tests is that they produce too many false-positive results. The CA 125 blood test does identify many cases of cancer, but the protein it measures can also be elevated by menstruation, pregnancy or conditions such as endometriosis. And most tumors found by ultrasound prove to be benign.

Some benign ovarian growths do need to be surgically removed because they may become twisted or grow so large they affect other organs *(see sidebar).* But many others may be related to the normal function of ovulation and will disappear on their own. Without a better way to distinguish among functional, benign and malignant tumors, women who have false-positive screening results are subjected to unnecessary anxiety and may undergo surgery that could have been avoided.

"Large-scale screening for ovarian cancer in women with no symptoms would be very costly," Fuller says. "In a group of 2,000 asymptomatic premenopausal women, only one will have cancer. Current screening tests would produce



*Arlan Fuller Jr., MD*

positive results for 20 to 40 women, so they would pick up far more false positives than true positives."

Among women at higher risk, however, the ratio of false positives to true positives goes down, which could make screening tests more useful. Therefore, a major research goal is finding better ways to identify those at risk. "Unfortunately, because they often develop in tissues lining the ovary or the abdominal cavity, most of the cancers we find today have already spread," Fuller says. "The more we can focus on patients at higher risk, the better our chance of finding their cancers earlier. And we hope that the research currently being pursued by us and others will allow us to find tumors earlier, when they are more treatable."

Carlson adds: "The concern that many women have about ovarian cancer is probably out of proportion to their true risk. Women who don't have a family history, especially those who either have been pregnant or used oral contraceptives, can really take this off their list of things to worry about. We know how important it is to carefully watch the women from families with a lot of cancer. It's the middle group — those with only one or two affected family members — for whom we need more information about the best screening strategies."

## *This tumor was not so benign*

THE NEWS that an unusual growth is "benign" is always a relief. But just because a tumor is not malignant, does not mean it cannot cause trouble.

One type of benign ovarian tumor has the potential to grow so large that it can seriously crowd adjacent structures in the body. It is not uncommon for these growths, called mucinous cystadenomas, to reach a diameter of 12 to 15 inches. This summer, MGH surgeons removed a 173-pound tumor — one of the largest on record — from a Boston-area woman. The largest such tumor, reported in 1902, weighed more than 300 pounds.

The tumor grew undetected for many years because the patient had been overweight most of her life. In addition, she avoided seeing doctors because, as a child, she had been sexually abused by a physician. But last fall the woman knew she had a problem when her abdomen became increasingly swollen despite the loss of 60 pounds through dieting. Still she delayed seeking medical attention for several months, during which her weight increased from less than 200 to nearly 350 pounds.

Eventually the tumor began to block the flow of blood from her legs back to her heart, and she developed severe swelling of the legs with cellulitis, an infection of the skin and soft tissues. The infection led to painful leg ulcers, and when she had difficulty walking she finally sought help from a local internist. The doctor diagnosed the cellulitis and the tumor, persuading her to seek further medical attention. He referred her to Arlan Fuller Jr., MD, chief of Gynecologic Oncology at the MGH, who removed the tumor in a three-hour operation.

There is no way of knowing how long this tumor, which measured more than three feet across, was present, Fuller says, although similar tumors have taken as long as 15 years to grow to a comparable size. As is characteristic of such growths, it was largely composed of fluid and did not extend into surrounding organs. During the operation, the surgeons drained 68 liters of fluid from one of several cysts, which reduced the tumor's weight to 22 pounds.

After some additional plastic surgery to remove excess skin around her abdomen, the 44-year-old patient is looking forward to returning to a normal life. "I'm going to be able to do things like skiing I haven't done in years," she says. "Everyone at the MGH has been fantastic. For so many years I was frightened to go to a doctor because of what happened to me, but I've learned that 99 percent of health professionals are wonderful people who are there to help you. I can't say enough about them."

Fuller explains that situations in which patients delay seeking necessary medical care because of past trauma, happen more frequently than one might think. "There are two lessons we can learn here," he says. "Patients with problems like this need to know it's never too late to get help. Moreover, all health care professionals must be sensitive to possible reasons why a patient did not seek care in the past. We must all do what we can to help them deal with the physical and emotional effects of past trauma." ■

### *Targeted treatment*

When cancer is diagnosed, treatment depends on several factors. Surgical removal of the tumor is always the first step, and chemotherapy is added when the cancer has spread or if microscopic examination shows a more aggressive type of tumor. "It's important to start chemotherapy as soon as possible," Fuller says. "You don't want to take out a large tumor and then give any remaining cells a chance to grow back. We're developing better nutritional support programs to help our patients quickly recover from surgery and start chemotherapy right away."

He adds that coming to a facility like the MGH, which has a comprehensive program for the treatment and study of ovarian cancer, is a good idea for the patient and her family. "In addition to access to the latest surgical and medical treatments, we have resources to provide complete psychosocial support to patients and their loved ones."

A hope on the horizon for better treatment lies in biologic therapies, natural substances that selectively interfere with processes required for a tumor's growth. Along with Patricia Donahoe, MD, chief of Pediatric Surgery at the MGH, Fuller has been working on studies of Mullerian inhibiting substance (MIS), which normally acts during embryonic development. "Several structures of the female genital tract — the uterus, cervix and Fallopian tubes — develop from an embryonic structure called the Mullerian duct," he says. "MIS inhibits that development in male embryos."

The vast majority of ovarian cancers grow out of epithelial tissues, which line the abdominal cavity, and grow in a way that recapitulates the development of the Mullerian duct, Fuller explains. He and his colleagues hope that MIS may be able to destroy these cancers just as it destroys the Mullerian structures, and some of their preliminary laboratory research has had promising results.

If biologic therapies prove successful, the resulting treatments should cause fewer unpleasant side effects because they will be directed toward only the cancer cells and will have little effect on healthy tissue. "Stopping the growth of cancer cells is like trying to turn off a ringing alarm clock," Fuller says. "You can hit it with a hammer — which is what we do now with chemotherapy — or flip the switch. We're looking for the switches." ■

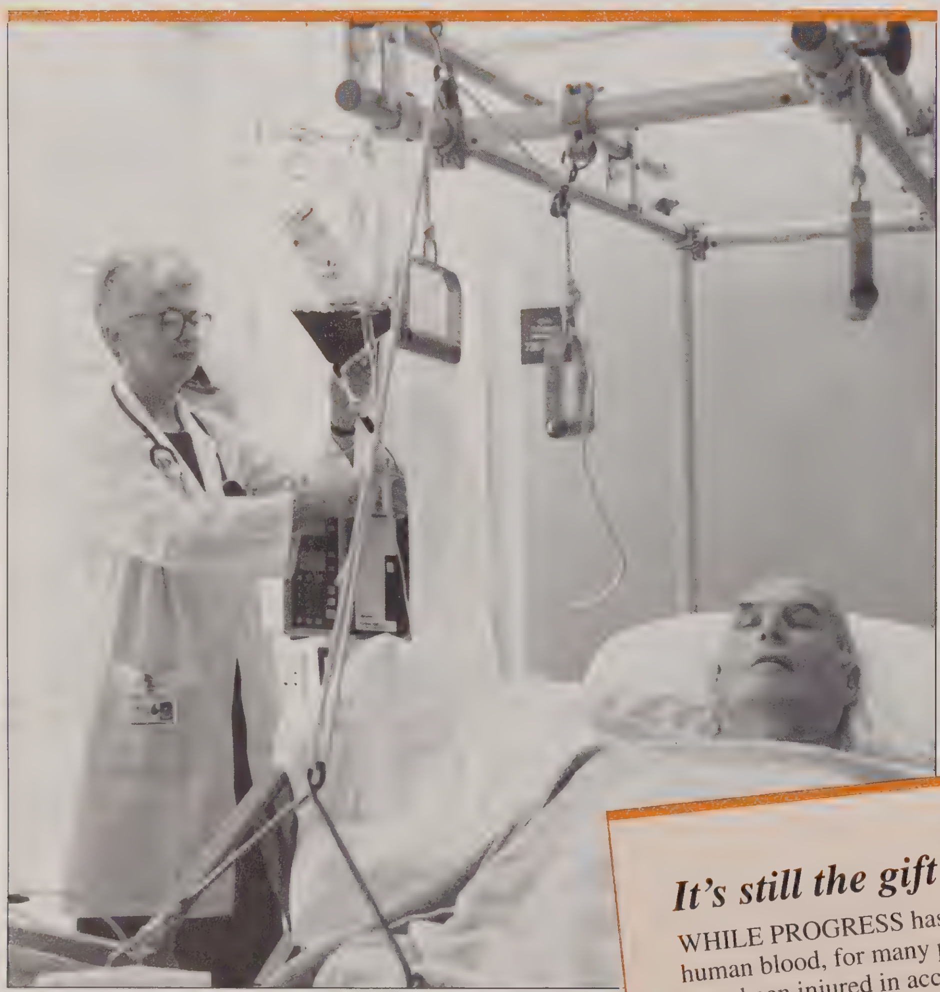
### Reducing the need for blood transfusion

# Only when absolutely necessary

IT IS A POWERFUL medical tool that saves lives. Like many drugs it can have side effects, and on rare occasions it carries dangerous infections. It can be costly and is occasionally in short supply. And there is currently no substitute for this precious fluid: human blood.

The MGH has one of the largest hospital-based blood banks in the country, annually transfusing more than 56,000 units of blood components — including red cells, platelets and plasma. Today a major effort by the Blood Transfusion Service and several cooperating departments is focused on reducing that number.

"The blood supply is probably safer now than it ever has been," says Christopher Stowell, MD, PhD, director of the MGH Blood Transfusion Service. "But because of the slight, although real, risk of transmitting an infection, and because other problems, such as allergic reactions, can occur in the course of a blood transfusion, we are working to limit the use of donor blood to only those situations in which it is absolutely necessary."



*Joan Carven, RN, research nurse in the Blood Transfusion Service, administers an experimental blood substitute to a patient recovering from orthopædic surgery. The product contains hemoglobin purified from the blood of cattle.*

Three specific strategies are reaching toward that goal. The first is simply not to give transfusions to many patients who might have received them in the past. "We now know that most patients do just fine without transfusions. Their hematocrits [the level of red cells in the blood] don't have to be as high as we used to think," Stowell says.

When a patient is scheduled to have an operation or procedure that probably will require additional blood, often the second strategy can be called into play: use of the patient's own blood. During the weeks before hospitalization, patients can donate units of their own blood, which are stored in the Blood Bank for their exclusive use. At the MGH, about 2,500 units are collected each year for what is called predeposit autologous transfusion.

But not everyone can donate his or her own blood. The option clearly is not possible for emergency surgery. Other patients should not risk the temporary reduction in oxygen-carrying red blood cells that follows a donation or have other factors related to their medical condition that rule out donation.

In such instances, the third strategy—salvaging some of the blood lost during an operation—applies. Special mechanical devices to collect, filter and return blood to the patient during an operation have become increasingly sophisticated and efficient.

Another operating-room technique called hemodilution has been around for decades. After the patient is anesthetized,

## It's still the gift of life

WHILE PROGRESS has been made in reducing the need for donated human blood, for many patients there still is no substitute. People who have been injured in accidents, some surgical patients, and those who undergo powerful anticancer treatments may all need the lifesaving components that can only be found in human blood.

Healthy volunteer blood donors are essential to maintaining a blood supply that is safe and available whenever patients need it. The MGH Blood Donor Center is open Monday through Thursday, 8:30 am to 7:30 pm, and Friday from 8:30 am to 4:30 pm. For more information or to make an appointment to donate, call (617) 726-3620. ■

several units of blood are removed and stored. Infusions of saline or protein solutions replace the removed fluids, so any blood lost during the operation contains fewer blood cells. When the surgery is complete and bleeding is stopped, the removed blood is reinfused into the patient, replenishing the supply of blood components.

"We've been working over the past 20 years to reduce blood utilization in operations that have high blood loss, such as cardiac surgery," says Michael D'Ambra, MD, a cardiac anesthesiologist. "But we've really reached the limit of what we can do with hemodilution and mechanical blood retrieval."

Fortunately, new options — several of which have been developed through MGH research — are becoming available. One is the use of erythropoietin (EPO), a natural hormone that stimulates the body to produce red blood cells. If EPO is administered to patients for several days before surgery, the number of red cells in the blood increases. The patients actually "store" extra blood in their own bloodstreams.

A current study conducted by D'Ambra and other MGH colleagues to look at the use of EPO in combination with doses of iron before cardiac surgery is showing promising results. The researchers have found that a week of combined treatment can generate as many new red cells as would be received in two or three units of blood. Stowell and several colleagues are conducting a similar study in orthopædic patients.

Other new techniques focus on preventing blood loss during and after surgery. One utilizes a drug called aprotinin, administered during surgery, and is proving useful for certain patients with known bleeding problems. Traditionally, such patients received platelets or blood plasma, but aprotinin may work better than traditional therapy.

"Aprotinin appears to augment the body's natural clotting system so that the incision does not bleed when the surgeon operates," D'Ambra says. "With aprotinin, we've also been able to stop bleeding that has not responded to blood component infusion."

Using all currently available techniques, the MGH is able to offer many patients what D'Ambra refers to as "bloodless surgery" for procedures that have traditionally required transfusions. One group of patients for whom that option is essential is Jehovah's Witnesses, whose faith forbids them to receive any human blood products whatsoever — even their own.

Also being investigated at the MGH is a possible replacement for human red blood cells. Produced by the Cambridge-based biotechnology company Biopure, the experimental material consists of hemoglobin (the oxygen-carrying molecule in red cells) purified from cattle blood. It does not need to be carefully matched to the recipient, as human blood must be, and can be stored for a longer period of time.

Stowell says that safety tests of the substitute material in human volunteers are being conducted at the MGH and elsewhere. If no negative side effects appear, the next step will look at how effective it is in carrying oxygen throughout the bloodstream.

"Blood substitution research today is concentrating on the oxygen-carrying function of the red cells; that will probably be the easiest nut to crack," he says. "Replacing some other components is going to be much more difficult. We already have genetically engineered versions of proteins like factor VIII, which is missing in the blood of people with hemophilia. But coming up with a substitute for platelets — which control blood clotting — is going to be really tough."

The need for platelets will actually increase in the future, as more cancer patients are treated with aggressive chemotherapy and bone marrow transplants — techniques that require platelet replacement. "I think we're going to be looking at human donation as a necessity for many years to come," Stowell says. ■

# MGH team ready to seek answers on breast cancer gene

IT WAS front-page news in papers across the country and around the world: "Scientists find breast cancer gene." The September announcement that the gene called BRCA1 had been found by scientists in Utah and North Carolina ended an intricate search. But like many discoveries, it raised a whole new set of questions, questions that MGH researchers are now poised to take the lead in answering.

"A couple of years ago, it became clear that many inherited cases of breast cancer were associated with mutations to a gene located somewhere on a small region of chromosome 17," says Stephen Friend, MD, PhD, director of the MGH Center for Cancer Risk Analysis. "Researchers at six institutions were actively searching for this gene. Because any one of those groups was capable of finding the gene, we decided to focus our efforts on answering some of the questions that would follow the gene's discovery."

One of the most important such questions is exactly how large a role this gene plays in the incidence of inherited breast cancer, particularly in women who develop the disease before age 50. The original evidence pointing to the existence of BRCA1 was found by studying families in which breast cancer, and sometimes ovarian cancer *(see story, page 1)*, occur with terrifying frequency. More than half the women in each generation may develop one of these cancers at a relatively early age.

*Ingrid Hoover (foreground) and Erin O'Neill, research assistants at the MGH Center for Cancer Risk Analysis, load blood samples into a genetic sequencer that will screen them for possible breast cancer-related genes.*

But there are families in which breast cancer is clearly inherited, but not with such prevalence. Does BRCA1 have a role in these inherited cancers? And among the families with a high incidence of cancer, is it the only gene responsible?

In preparation for tackling these and other questions, Friend and his staff have assembled a genetic library of blood samples from 400 women who developed breast cancer at age 40 or younger. The samples will allow them to search for

*(Continued on Page 8)*

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mutations in any gene associated with breast cancer. That ability to test any number of genes in the same set of samples — essentially retesting the same patients — will provide scientifically reliable information on exactly how important each gene is in breast cancer.

"About 10 percent of all women who get breast cancer inherit a susceptibility to the disease," Friend says. "We're now asking what portion of that 10 percent is associated with this gene. Some have guessed that it is about half, but now we have a chance to verify that number. We also expect that a higher percentage of young women who develop cancer will have an inherited susceptibility and that BRCA1 may play a much larger role in that group."

He adds that, while such percentages could appear to minimize the importance of this gene, looking at the statistics in other ways gives a more accurate picture of its impact. "We're talking about this gene's being involved in the development of tens of thousands of cases of cancer every year. And for women who belong to families that carry a mutated version of this gene, knowing whether they or their daughters are actually affected can be a very important piece of information."

Barbara Smith, MD, PhD, director of the MGH Comprehensive Breast Health Center, says: "Right now a lot of women who have a relative with breast cancer are treated as if they are at high risk themselves, which causes a great deal of anxiety for them, their families, and their physicians. The identification of the BRCA1 gene is the beginning of our being able to much more precisely estimate breast cancer risk. It will be wonderful to spare low-risk family members any unnecessary treatments and to give appropriately careful attention to the women who are truly at high risk."

Most researchers estimate that a practical blood test for BRCA1 mutations will not be available for a couple of years, and the kind of information Friend's group will be gathering is essential to developing such a test. But when the test is ready, it will open up another thorny set of issues.

> **"We're talking about this gene's being involved in the development of tens of thousands of cases of cancer every year."**

Deborah MacDonald, RN, MS, nurse genetic specialist with the Center for Cancer Risk Analysis, also works with women at risk for cancer through the Breast Health Center. She explains that any genetic testing must be accompanied by careful counseling so patients understand what the information does and does not mean.

"Having a BRCA1 mutation would greatly increase a woman's risk, but it would not make it absolutely certain that she will develop breast cancer. The fact that she is free from this mutation doesn't rule out her carrying other high-risk genes or having the same risk that applies to the general population," she says.

MacDonald adds that testing also raises a host of issues related to confidentiality. Would a prospective employer or insurance company have access to such information, and could it be used to deny a job or insurance coverage to an individual woman? "We already know of women who have been discriminated against because they've had breast cancer. With genetic tests for so many diseases on the horizon, society is going to need legal safeguards to keep this information confidential and to protect patients' rights."

Another major question about BRCA1 is how the mutation in the gene actually causes cancer and ultimately what is the gene's normal function in the body. Friend explains that this information could lead to quicker, simpler tests for a mutation, tests that directly measure the gene's function rather than search for a minute structural defect.

Even more important, understanding how the gene works could eventually lead to new ways of preventing or curing cancer. "The ability to restore whatever function goes wrong when this gene is mutated would allow us to directly attack the process leading to cancer development," he says. "That may be the real hope for women whose families have been haunted by this devastating disease." ■

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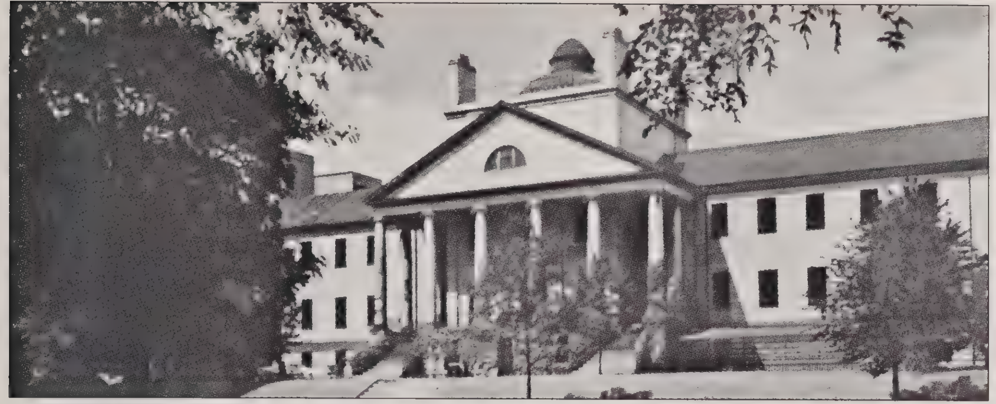

# MGH News

Massachusetts General Hospital, Boston, Massachusetts

December 1994 - January 1995

*Michaela Abby Mellen, the first child born in the new MGH Mother and Child Center*

## Opening of Mother and Child Center brings obstetrics back to the MGH

THE "MISSING SERVICE" at the MGH is missing no more. With the Nov. 1 opening of the MGH Mother and Child Center, a full range of obstetrical services became available at the hospital for the first time in about 40 years. And less than 24 hours after the units in the hospital's new Blake Building opened their doors, the first baby — a healthy girl — was delivered.

The opening culminated more than five years of planning, negotiation and hard work by hospital staff — including the members of the MGH's Vincent Memorial Obstetrics and Gynecology Service and the nurses and other professionals associated with the center's ambulatory and inpatient activities.

Isaac Schiff, MD, MGH-Vincent chief of Obstetrics and Gynecology, recalls that initial efforts began in the late 1980s, but it was not until 1991 that the hospital formally committed to begin offering prenatal care, labor and delivery services to MGH patients.

"For a long time, obstetrics at the MGH was but a gleam in the eye of a few dreamers who felt that a 'general' hospital that did not help bring people into the world but only cared for them when they were sick was perhaps a three-star general or even a four-star general, but not the five-star general hospital that it should be," Schiff says.

The Mother and Child Center is located on three floors of the newly constructed Blake Building. The Labor and Delivery Unit on Blake 14 features 11 private labor/delivery/recovery rooms, two suites for cesarean deliveries, and special admitting, observation and examination areas.

The Newborn Family Unit on Blake 13 features 21 private postpartum rooms. Newborns may stay with the mother in her room or be cared for by a family nurse in an adjacent nursery. The unit also features a special care nursery for infants who need extra attention but not the advanced services offered in the hospital's Neonatal Intensive Care Unit.

Schiff notes that while obstetrics falls under his service's umbrella, the new pro-

*(Continued on Page 6)*

## *Becoming pregnant is not always easy*

JULIE AND ROGER MELLO thought having a baby would be easy for a couple in their mid-20s, and they hoped to have two children by the time they reached 30. Now four years after deciding to start a family, they are finally expecting their first child. But the process has been anything but easy.

After trying to get pregnant for a year and a half, the couple sought the advice of a local gynecologist. He found that Julie's body was producing an antibody to her husband's sperm, a problem that would not resolve itself. "We did not feel defeated," she says. "Our attitude was, 'What's our next step; what do we have to do to conceive?'"

The gynecologist recommended artificial insemination, which would place Roger's sperm beyond the antibodies. After several failed attempts, the gynecologist referred the Mellos to Thomas Toth, MD, a physician in the Gynecologic Reproductive Endocrinology Division of the MGH's Vincent Memorial Obstetrics and Gynecology Service and director of the division's In Vitro Fertilization (IVF) Unit.

Infertility can have several causes: problems with eggs, sperm or embryo, difficulty with implantation and carrying to term, as well as combinations of factors. Improvements in the ability to pinpoint the underlying causes of infertility have been followed by an increase in the number and availability of corrective procedures. Although the Mellos initially believed their infertility was

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### INSIDE

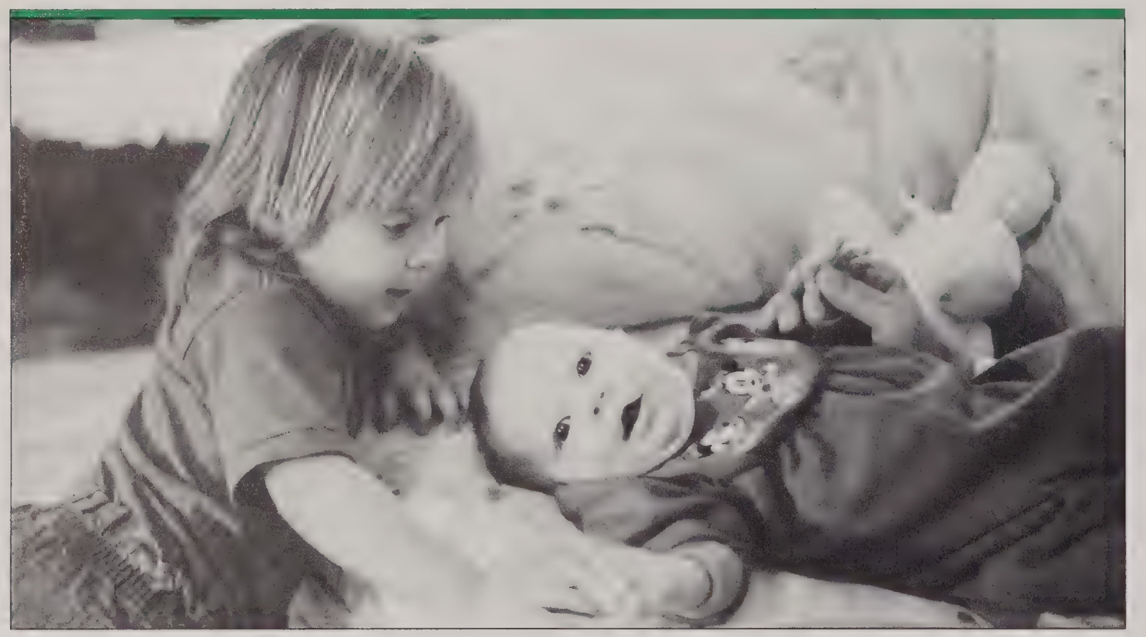
**MGH team helps critically ill infant**
*Page 2*

**Nurse midwives at the MGH**
*Page 7*

# *MGH team helps critically ill infant beat the odds*

THE SITUATION looked hopeless. For three weeks a team of doctors and nurses in the MGH Neonatal Intensive Care Unit (NICU) had been struggling to save newborn Amiera Agamy, but the infant's condition just kept getting worse. Her heart and lungs were being maintained by a machine, and an infection had affected her liver, kidneys and perhaps her brain.

Amiera's doctors decided on a last-ditch effort, a procedure that might help her heart pump more efficiently but had never been shown to help a baby in her precarious situation. Even with the procedure, the infant's chances for survival were slim.



*Two-year-old Deena Agamy is fascinated with her sister, Amiera. The infant recovered from a nearly fatal illness with comprehensive care from a team in the MGH Neonatal Intensive Care Unit.*

But today, Amiera is 4 months old and home with her family. Despite the ordeal of her first weeks of life, she appears to be developing normally and headed toward a healthy life.

Amiera's troubles began during her birth Aug. 17. Everything seemed normal when her mother, Ida Agamy, entered Emerson Hospital to have her second child. The fact that her labor was a few weeks early was actually welcomed; the baby would be smaller than expected, and she would try for a natural labor instead of the cesarean delivery she had with her first child.

But midway through labor, things suddenly began to go wrong. Agamy began bleeding profusely and suddenly felt that the baby was moving upwards in her abdomen. The fetal monitor showed a loss of the infant's heart rate. The doctors rushed Agamy into the operating room for an emergency cesarean and found that her uterus had ruptured.

Amiera was not breathing when she was delivered, and her heartbeat was very weak. The Emerson delivery team resuscitated her, but the infant was critically ill. She was transferred to the MGH, placed on a mechanical ventilator to support her breathing and received medication to strengthen her heart. Her mother stayed at Emerson to recover from her surgery and was discharged in a few days.

At first it seemed that Amiera would also recover quickly. The breathing tubes were removed and her parents were told she might soon be going home. But on the third day, her condition took a sudden turn for the worse. She developed a fever, and the function of her lungs began to deteriorate, evidence of an infection — probably a virus — that spread throughout her body.

Soon Amiera showed symptoms of myocarditis, an inflammation of the heart muscle, and pulmonary hypertension, a buildup of pressure in the lungs that impedes the normal flow of blood from the heart to the lungs. To keep her alive, the doctors placed Amiera on ECMO (extracorporeal membrane oxygenation), a machine that takes over the function of the heart and lungs. Partially developed and tested at the MGH, ECMO allows immature or damaged organs to rest and heal and is the preferred treatment for many respiratory diseases in newborns.

But even on ECMO, Amiera's condition did not improve. Because the technique requires the use of blood-thinning medication, a lengthy course of ECMO would put the infant at risk of internal bleeding. The team of doctors and nurses caring for Amiera, led by Leticia Castillo, MD, neonatologist, searched for another way to help her weakened heart and lungs recover.

The team began to consider a risky option, a procedure called a balloon atrial septostomy, which is experimental in a situation like Amiera's. The technique involves threading a catheter through a major blood vessel, into the heart and then through the wall separating the two upper chambers of the heart. A small balloon at the tip of the catheter is inflated, and when the catheter is pulled back through the wall, the attached balloon tears an opening between the two chambers.

Lars Erickson, MD, the pediatric cardiologist caring for Amiera, explains the theory behind the septostomy: "When the heart is weakened, it must fill with more blood than usual to stimulate the heart muscle to pump harder. A very weak heart, however, can become so overfilled that it actually pumps less well, setting off a downward spiral of further stretching and weakening of the heart.

"By tearing a hole between the two upper chambers of the heart, we can reduce the filling of each chamber and potentially reduce this downward spiral. But if we deprive the heart of too much blood, the patient could be much worse off," he adds.

With no other alternatives, the doctors discussed the procedure with Amiera's parents. Erickson explained that there were only two reports of infants like Amiera having the septostomy, and only one had survived. But the procedure was the only thing they could offer.

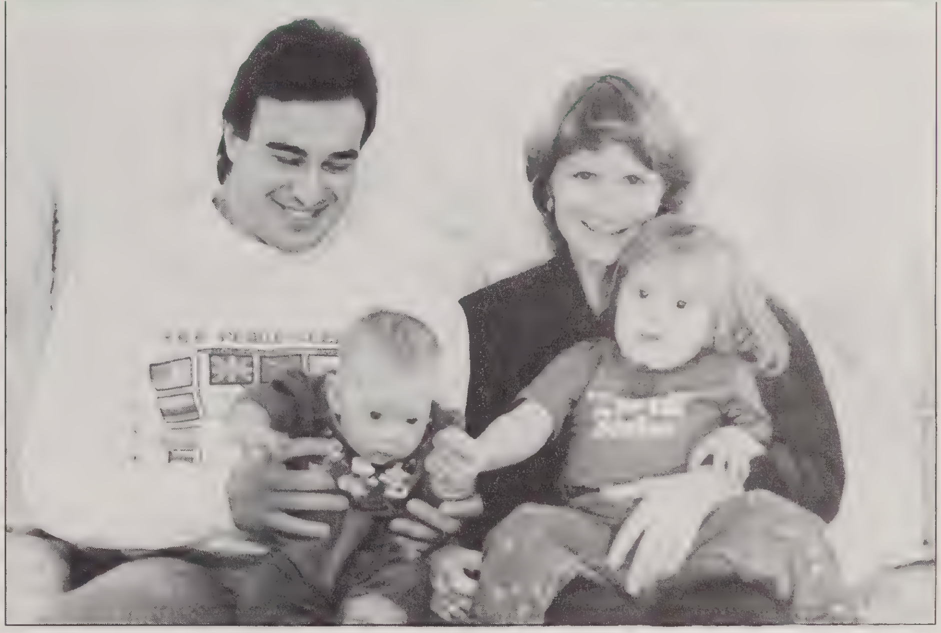
> **"It requires long hours — from doctors, nurses, everybody — of standing at the bedside, watching what is happening and thinking about how you can give your patient a little more time."**
>
> **— Leticia Castillo, MD**

"We told him to go ahead," Agamy says. "It was either that or let her die."

Erickson carried out the septostomy when Amiera was 3 weeks old. At first it did not appear to make much difference. There was some improvement in heart function, but the baby still required ECMO. Two days later, a CT scan showed evidence of bleeding in Amiera's brain. ECMO and the blood-thinning medicine it required would have to be discontinued before a fatal brain hemorrhage occurred.

"The doctors were very honest with us," Agamy says. "They didn't expect that Amiera would survive more than a few minutes after the ECMO was turned off."

But when the ECMO was removed, Amiera surprised everyone. Her heart beat very weakly at first, but over the next few hours it became stronger. Within days the organ's function was nearly normal. Continuing to receive mechanical ventilation, she steadily improved and by 6 weeks of age was breathing on her own.



*Healthy, happy and home: Parents Adel and Ida Agamy hold their daughters Amiera and Deena.*

On Oct. 19, Ida Agamy, a captain in the Army, and her husband, Adel, took 2-month-old Amiera home to Ft. Devens, Mass.

Amiera's doctors believe her recovery can be traced to a number of factors. Although it cannot be proved, the septostomy probably improved her heart function enough to get her through the most critical period. Also essential is the team approach taken by the many specialists working with the NICU staff.

"In caring for the very sick babies seen in the NICU, we have to be very aware of the possible consequences of everything we do," Erickson says. "Those of us working to improve heart function have to spend a lot of time talking with the neonatologists, the pulmonary specialists, the neurologists and everyone else involved in the care of these patients."

Castillo adds: "It's a delicate balance between medications that you have to give and the side effects they may have, which can be much more serious in a little baby. You pay a price for everything you do in the ICU, and you have to consider whether it's worth it to pay that price. It requires long hours — from doctors, nurses, everybody — of standing at the bedside, watching what is happening and thinking about how you can give your patient a little more time."

And time can make the difference for a patient like Amiera, Castillo says. "With critically ill adults, often the organs are too damaged to recover, even with mechanical assistance. But most children have basically healthy organs. If you keep them alive and give them enough time, they will come back."

Although Amiera now appears perfectly normal, she will be followed closely by the MGH team to watch out for any long-term effects of her illness. She will probably have a procedure to close the hole inside her heart when she gets older. But right now her parents and 2-year-old sister are enjoying every day with their "miracle baby," and they have nothing but praise for those they credit with saving her life.

"There can't be better doctors and nurses on the face of the earth than the folks at MGH," Ida Agamy says. "They treated us like intelligent adults; everyone without exception was really great. Their openness and compassion made this whole experience a lot more survivable." ■

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PHOTOGRAPHS: Pages 1, 2, 3, 6, 7 (top left) Susan McGreevey; page 4, Maria Sacco; page 5, Wendy Matarazzo; page 7, (top right) Jeff Thiebauth; page 8, Jeff Wdow.

# —It's not always easy to become pregnant

*(Continued from Page 1)*

caused solely by the sperm antibodies, additional factors would prove to be involved.

Late in 1992, Julie began follicle stimulating hormone therapy, which helps induce eggs to mature. During this process, the size of the follicle (the fluid-filled sac in the ovary that nurtures the ripening egg) is tracked via ultrasound every other day for 10 days of each menstrual cycle. For the Mellos, this meant leaving their home, one hour away from the MGH, at 6 am so they could complete the appointment and get to work by 9 am.

*Thomas Toth, MD, director of the MGH's Vincent In Vitro Fertilization Unit holds Matthew Sacco, son of Maria and Michael Sacco. Maria, an MGH employee, underwent a successful IVF procedure, and Matthew was born Feb. 13, 1994. Surrounding Toth are members of the IVF team, from left: Elsie Willant; Christine McNally, RN; Johnny Awwad, MD (standing behind Toth); Patti Micelli, RN; and Zuying Chen, MD.*

### *Emotional support*

According to Toth, comprehensive care for infertility must include emotional support. Frank, honest communication can help couples cope with issues ranging from concern about costs, to the possibility of multiple births, to failed attempts to conceive.

These patients face many issues similar to those in other stressful situations. Ellen Feldman, LICSW, a staff social worker specializing in infertility, notes that some issues, like sexuality, are more specific to infertility and can negatively affect an individual or couple's self-esteem.

"It is hard for most people to understand how difficult dealing with infertility can be," Feldman says. "I try to appreciate where the couple is coming from, their style, and to help them cope with and reduce their stress around infertility."

Julie says that after several months she got angry, and she voiced her frustrations, doubts and disappointments to Feldman. "I was looking for a guaranteed procedure," Julie says, "even though I knew deep down inside there wasn't one."

In January 1993, Julie had a laparoscopy, an outpatient diagnostic procedure. By inserting a surgical instrument through a small incision below the naval, Toth was able to look directly at her ovaries and the exterior of her fallopian tubes and uterus. The procedure revealed that Julie's ovaries and tubes appeared normal but that she had mild endometriosis. Although Toth believed the endometriosis probably was not hindering conception, he removed it to be sure.

After a series of setbacks with hormonal therapy treatments, the Mellos felt their last option was to try IVF.

"We had been on a roller coaster of disappointments and complications for two years and had resolved IVF was the last procedure we were going to try," says Julie.

### *A highly regarded service*

Although the IVF Unit at the MGH is relatively new — it was established in 1992 — it is highly regarded, and patients whose cases are especially complex and difficult are often referred to the team. Despite that challenge, the unit has achieved a 30 percent success rate with IVF, well above the national average of around 18 percent.

"Identifying the reasons for infertility can be a complex process," says Toth. "Finding the balance between intervening too little and doing too much can be difficult and can try the patience of even the most determined couple."

The physicians, nurses and other members of the unit's staff take a highly individualized approach to each couple's situation. "Everyone involved is very dedicated to the care of our patients," says Isaac Schiff, MD, chief of the MGH's Vincent Memorial Obstetrics and Gynecology Service. "Each patient is treated as an individual and with sensitivity to her specific needs."

As part of an academic medical center like the MGH, the unit can provide the highest level of coordinated care possible. Top-notch support services like anesthesia are readily available on site. Women pursuing IVF can be monitored and treated for any additional medical problems. The frequent laboratory tests necessary throughout many assisted reproductive technology procedures can be expertly handled in-house by the MGH Reproductive Endocrinology Laboratory, under the auspices of the Department of Medicine.

"The IVF Unit is committed to research that will improve conception rates through assisted reproductive technologies," says Keith Isaacson, MD, director, Gynecologic Reproductive Endocrinology Division. "For example, we currently are collaborating on several research projects, one to search for serum markers that predict IVF outcome and another to freeze eggs from cancer patients before they receive radiation or chemotherapy."

The Mellos began the IVF process with hormone therapy to stimulate the growth and maturation of follicles and control the timing of ovulation. Such precise control allows the maturation of several eggs, which are retrieved before they are spontaneously released. For this phase of treatment, Roger learned to give his wife hormone injections.

*Julie and Roger Mello*

"I didn't mind giving the injections, but I felt bad about the side effects the medication had on Julie," he says. "Throughout this whole process, we went through different stages; there were times when I wanted to stop and Julie wanted to continue, and then the reverse. But by trying IVF, we both felt we were doing everything we could."

After ovarian stimulation, patients are monitored by ultrasound and blood tests to determine the optimal time to retrieve eggs. The retrieval is accomplished by ultrasound-directed needle aspiration, a minor surgical procedure that enables the physicians to accurately guide a needle into follicles and gather eggs.

The eggs and a semen sample that has been processed to obtain the most motile sperm — those most able to move about, and therefore most likely to fertilize an egg — are placed together, and fertilization occurs in the laboratory. The final step in IVF is transferring the embryo into the woman's uterus.

Two weeks after their embryo transfer, the Mellos went to the IVF clinic for a pregnancy test, and on Aug. 15 they learned that their efforts had paid off — Julie was pregnant.

"It feels great. It's amazing, and I just can't believe it," she says. "The people at the IVF Unit are some of the finest individuals. They are warm, caring and kind. I've never been treated so well at any other hospital. They genuinely care. We will be grateful to them forever."

Now Julie is preparing for the springtime delivery of her baby under the care of Robert Blatman, MD, a specialist in maternal-fetal medicine in the MGH's new Vincent Obstetrics Program.

"We've now moved to a different MGH team, but the caring attitude is the same," says Julie. The couple says they would try IVF again. "We want to build our family however we can," she says. ■

## *Available IVF techniques*

THE SCIENTIFIC ADVANCES that make assisted reproductive techniques possible are constantly breaking new ground. The MGH's Vincent Memorial In Vitro Fertilization (IVF) Ethics Committee evaluates all new approaches to ensure that they are implemented appropriately and to address the complex issues surrounding reproduction. Below are the techniques offered by the Vincent Memorial IVF Unit.

### *IVF-ET (In Vitro Fertilization-Embryo Transfer)*

This is probably the best known and most widely used assisted reproductive technique. Mature eggs are removed from a woman's ovary and fertilized by sperm outside of her body. After a fertilized egg divides in the laboratory for two days, it is placed back into the uterus of the woman who produced the egg.

### *GIFT (Gamete Intra-Fallopian Transfer)*

Often used in cases of unexplained infertility or when it is difficult to determine whether the sperm and egg ever meet. A mature egg is retrieved and placed together with sperm from the woman's partner. The sperm-egg mixture is then placed into the fallopian tubes where fertilization may take place.

### *ZIFT (Zygote Intra-Fallopian Transfer)*

In this procedure, a hybrid of IVF-ET and GIFT, the egg is fertilized in the laboratory and then placed in the fallopian tubes for the very early stages of development.

### *Micromanipulation*

Micromanipulation can be used when sperm-related problems have made fertilization difficult or impossible. It also can be used to manipulate an embryo, improving the likelihood that it will implant. This is especially helpful for patients who have experienced repeated IVF failures.

Other techniques, including egg or sperm donation and cryopreservation (freezing and storage of eggs, sperm or embryos for later use), are also available at the MGH.

# —Obstetrics comes back to the MGH

*(Continued from Page 1)*

gram involves the entire hospital and relies on the long-established excellence and support of departments such as the Children's Service, the Pediatric Surgical Service, Nursing, and programs in infertility treatment, genetic counseling and ultrasound.

*In the MGH Chelsea Memorial Health Center, Isabel Aviles measures and weighs Magaly Vargas during her first prenatal care visit.*

### *Collaboration and choice*

Within the Mother and Child Center itself, collaboration and integration of services is the rule. Both nurse midwives and obstetricians are available to provide prenatal care and deliver babies, and a woman expecting a normal pregnancy can choose the type of provider she wishes to see. The close partnership between midwives and obstetricians in the MGH service means that even when a patient develops a minor medical problem, the midwife may continue to be involved in her care. *(See story on next page for more on nurse midwives at the MGH.)*

Offering choices to an expectant mother is another guiding philosophy. In addition to the type of provider she wishes to see, a woman can choose how her pain will be managed, her birth position, how much time she will spend with the newborn, and when she will receive visitors.

"Our staff is keenly aware that each child-bearing experience is unique," says Fredric D. Frigoletto Jr., MD, chief of Obstetrics. "We want to ensure that individual needs and preferences are met whenever possible."

The hospital's three community health centers in Charlestown, Chelsea and Revere are integral parts of the new program. While some patients with established pregnancies are continuing to be cared for by the non-MGH obstetricians and midwives who have provided care at the centers for years, new patients and those who have chosen to deliver at the MGH are now being seen by members of the Mother and Child Center staff. By next spring, MGH staff will provide all pregnancy-related services at the health centers.

"The nurse practitioners who have been providing prenatal care in the centers do an excellent job," says Alessandra Peccei, MD, the MGH obstetrician who is now seeing health center patients. "They have established programs that meet the specific needs of their patients, and the knowledge they and the other staff members have of the local community is a real help to those of us who are new to the health centers."

Frigoletto adds: "All of us have worked to make our services as user-friendly as possible, both on the main campus and in the health centers. While health center patients will receive care in their local communities whenever possible, they also have full access to the programs and specialty services at the hospital."

Among these services are family education programs, including classes in childbirth and infant care as well as special sessions designed for the infant's siblings and grandparents. Available follow-up care includes postnatal home visitation by a nurse who can reinforce information learned in prenatal classes and help family members adapt to their new roles.

### *Designed for convenience*

Also designed for patient convenience is the ambulatory obstetric suite, which opened on Blake 10 in December. All prenatal care and diagnostic services are now located on the same floor — including genetic counseling, obstetrical ultrasound, nutrition, social services and counseling for those with high-risk pregnancies. The ambulatory suite is located right next to the new quarters of the MGH Women's Health Associates.

Collaboration also characterizes the relationship between the MGH center's staff and their counterparts at Brigham and Women's Hospital, affiliated with the MGH through Partners HealthCare System, Inc. Not only are the staff members sharing information about patient care and research developments, but a new joint obstetrics/gynecology residency also has been formed. Established in February, the combined program is governed equally by both hospitals and is already regarded as a national leader.

"Because of the diverse and prestigious programs operated by both hospitals, we are able to attract superb resident physicians to provide top-notch care for our patients," Schiff says. "Everybody is benefiting from this combination of strengths." ■

*(Top) At an open house to celebrate the opening of the MGH Mother and Child Center, Toni Hurton explains obstetrical ultrasound to a young visitor.*

*(Bottom) Michelle Finn, RN, leads a childbirth preparation class.*

*Cutting the traditional ribbon to open the MGH Mother and Child Center are (from left) Isaac Schiff, MD, chief of the MGH's Vincent Memorial Obstetrics and Gynecology Service; Ferdinand Colloredo-Mansfeld, chairman, MGH Board of Trustees; Mr. and Mrs. Curtis Blake, donors for the Blake Building; Samuel O. Thier, MD, president, The Massachusetts General Hospital; Lewis Clark, chairman, Vincent Board of Trustees; and Fredric D. Frigoletto Jr., MD, chief of Obstetrics.*

# *Midwives vital to MGH Obstetrics Service*

FOR MANY PEOPLE, a midwife is associated with folk medicine, past and present. Some picture an almost mythical figure who ministered to women on the American frontier. Others see an unconventional clinician delivering babies in homes. Neither image is entirely wrong, but both are incomplete. Nurse midwives are as current and vital a part of modern, established obstetrical practice as obstetricians themselves.

The nurse midwife's image is so out of date because for much of this century they were forbidden to practice in many parts of the United States. Although many still practiced outside the medical establishment, it was not until 1977 that nurse midwives could legally deliver babies in Massachusetts.

The profession began to make a comeback approximately 30 years ago, says Sherrin Langeler, CNM, director of Midwifery at the MGH. "Women were beginning to question some aspects of their obstetrical care," she says. "For instance, only 25 years ago some women were given 'twilight sleep' during delivery. They were drugged so heavily that when they woke up, they had already had the baby. Because of practices such as this, women in the '60s began demanding more choices in their obstetrical care."

> **"We wanted to create a user-friendly program in which women could have their babies with as little intervention as possible. I knew from the start that nurse midwives would be an essential component of any such program."**
>
> **— Isaac Schiff, MD**

Nurse midwives offered the options many women were looking for in their care. That is why, when envisioning the return of an obstetrics service to the MGH, Isaac Schiff, MD, chief of the MGH's Vincent Memorial Obstetrics and Gynecology Service, always pictured a program in which some deliveries were performed by nurse midwives. "We wanted to create a user-friendly program in which women could have their babies with as little intervention as possible," Schiff says. "I knew from the start that nurse midwives would be an essential component of any such program."

Despite growing popularity, midwifery still suffers from many misconceptions. One of the most enduring is the belief that nurse midwives and obstetricians have a competitive relationship. Not so, at least not at the MGH. There are few restrictions on the care nurse midwives may provide. In fact, in addition to delivering babies, they perform many of the same functions as obstetricians: providing care from the prenatal period, through labor and delivery, to postpartum follow-up. Their services include patient education and counseling, writing prescriptions, administering local anesthetics, and performing minor surgery that may be necessary to facilitate delivery. To practice, a nurse midwife must be an experienced registered

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## — Nurse midwives

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nurse and pass a national certification exam.

"The difference between obstetricians and nurse midwives begins and ends with training," says Fredric D. Frigoletto Jr., MD, chief of Obstetrics at the MGH. "Physicians are trained to address high-risk deliveries with such interventions as surgery. Nurse midwives concentrate on essentially normal or low-risk deliveries. However, if complications arise, an obstetrician is always immediately available. In many instances, both professionals can collaborate to provide the best care for mother and baby."

While low-risk patients may choose to be cared for by an obstetrician at the MGH, many have been opting for one of the hospital's eight nurse midwives. "Many are choosing out of a desire for a highly personal, low-intervention delivery," Langeler says. "Others are choosing us on the recommendation of someone whose baby was delivered by a nurse midwife. There is also a certain population that definitely wants to be cared for by a woman."

Diverse patient populations make the obstetrician/nurse midwife model particularly appropriate to a large academic medical center such as the MGH, which draws all types of patients. High-risk patients often require time-consuming tests and procedures, which quickly fill obstetricians' schedules. Because they care for low-risk patients, nurse midwives are able to spend more time on a one-to-one basis with each patient.

"From a patient's very first prenatal visit, we actively listen to her concept of an ideal birth, and as much as possible, we personalize her care to help bring about that outcome," says Langeler. "If she doesn't know exactly what she wants in a birthing experience, we teach her about the options available so she can begin to develop her own expectations.

"Women who are expected to have normal deliveries can be made to feel 'boring' at some large academic medical centers where so often the focus is on high-risk patients," she continues. "At the MGH, nurse midwives are here to prove that patients can have a very normal, intimate, loving birth in the middle of a tertiary care center."

Nurse midwives are currently seeing patients for outpatient prenatal care on the MGH main campus and at the MGH Chelsea Memorial Health Center. They will begin seeing patients at the Bunker Hill Health Center and Revere Health Associates in 1995. ■

*Sherrin Langeler, CNM, director of Midwifery at the MGH.*

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Massachusetts General Hospital, Boston, Massachusetts

February/March 1995

# Changing times in emergency medicine

IT'S 3:12 on a Sunday morning in the MGH Emergency Department. Four auto accident victims have just come in, all with multiple injuries. The physicians and nurses on the trauma team move as a unit from bed to bed, assessing, treating and comforting. On the other side of the wall, a 1-year-old asthma patient is given a treatment that may help him (and his parents) breathe easier. And down the hall, tucked into a corner of the nonacute area, a middle-aged woman sleeps soundly while her physician arranges to admit her for assessment of a benign brain tumor.

"At the MGH, emergency medicine is in a process of evolution," says Alasdair Conn, MD, chief of Emergency Services. "We get fewer walk-in, or minor injury, patients than we did in the past. We are seeing more patients with traumatic injuries, cardiac arrests and strokes. And with that increase comes the need to expand and fine-tune the department's physical layout, systems and staffing." (The hospital recently received reverification as a Level One trauma center.)

One of the most essential changes has been physical, resulting in the construction of a new facility *(see sidebar, page 5).* Other changes are more subtle. For example, previously all but the most critically ill patients registered upon arrival, were sent to triage for assessment, and then waited their turn to be seen by a physician. Now, patients see a triage nurse before registering. The nurse immediately assesses their condition — asking questions and taking temperature, pulse and blood pressure — and then refers patients to the most appropriate treatment area. This new system helps identify those patients who need more immediate medical care.

Patients have changed too. "Emergency medicine very much requires a team

*(Continued on Page 4)*

*The new MGH helipad atop the Blake Building — the only such facility at a Boston hospital — shaves precious, sometimes lifesaving, minutes off the time required to transport critically injured patients to the Emergency Department.*

## *Making her own decisions*

FOR ALL CHILDREN, the process of growing up requires developing the self-awareness and independence to make important decisions about their lives and futures. For children with chronic illness those decisions may be complicated by physical limitations. While continuing to rely on the support of her family and caregivers at the MGH, Nancy Digeso of Cambridge, now 20 years old, is taking charge of the treatment she receives for a rare illness.

Early one morning when she was 5, Nancy woke up feeling dazed and wobbly and called to her parents for help. "We were sitting at the kitchen table that Sunday morning," says Maria Digeso, Nancy's mother. "We went to her and saw her spin and fall when she tried to stand up. Her face was twisted, with her mouth to one side, and one eye was drooping."

The terrified family rushed the child to an emergency room, where physicians offered a possible diagnosis of encephalitis. Nancy quickly recovered from her mysterious symptoms, but similar incidents recurred over the following years. Several diagnoses were suggested, including multiple sclerosis and Rocky Mountain fever. Another possibility was polyarteritis

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# —Making her own decisions

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nodosa, a rare disease causing inflammation of small arteries. After three years of diagnostic dead ends, a school nurse who had observed Nancy through the years of frustration recommended that the child see a pediatric neurologist whom she considered the best — Elizabeth Dooling, MD, of the MGH's Pediatric Neurology Unit.

"When I first met Nancy, she had red, bumpy skin lesions on the soles of her feet, her hands and arms, which were very painful," recalls Dooling. Nancy was treated for the lesions and recurring fevers. Because lesions can be a symptom of polyarteritis nodosa, the possibility that she had the disease grew stronger.

*Physical therapy helps Nancy Digeso (left) gain strength and mobility. Pictured along with Nancy and Prudence Markos, PT, is Kathy Belton (right). She and Nancy became friends nine years ago and the two often schedule appointments together.*

### Strokes confirm rare condition

In 1985, Nancy, then 11, was doing her homework when sudden weakness caused her to drop the pencil from her hand. Her left leg buckled, her left hand clenched, and the right side of her body felt unsteady. Nancy was hospitalized at the MGH, where an MRI exam — a technique that had only recently become available — revealed that she had blockages in arteries on both sides of her brain, what are commonly referred to as strokes.

The MRI also showed that Nancy had suffered smaller strokes earlier in life — evidence to confirm a diagnosis of polyarteritis nodosa. The disease's characteristic inflammation can cause arteries in any part of the body to narrow, hindering proper circulation and causing infarcts, small areas of tissue damaged from lack of oxygen. Inside the brain, these infarcts cause the kinds of symptoms Nancy had experienced for years.

One of the reasons it had taken so long to confirm the diagnosis of polyarteritis nodosa is because the illness is so rare. Fewer than 20 children in the world have been diagnosed with the condition. Nancy is Dooling's first and only such patient.

Once Nancy's problem was identified, Dooling and John Mills, MD, an MGH pediatric rheumatologist, started her on a treatment regimen of steroids to reduce inflammation and chemotherapy to increase the rate at which old cells die. The treatment also increases the development rate of new cells, which may be less prone to inflammation.

Both treatments can have serious side effects, however. Steroids may cause weight gain, acne and bone thinning after long-term use, making fractures more likely. When the cytotoxic agents used in chemotherapy gave Nancy problems with her kidneys and bladder, her medication schedule was changed. Over the next year, symptoms of her arteritis subsided. Although she experienced several small strokes since treatment began, none have been as serious as those she had at 11.

### Some difficult adjustments

Damage from the larger strokes affected Nancy's speech and movement, and she began feeling uncomfortable at school: "The kids were pretty mean. Even my old friends didn't want to be around me," she says. "Dealing with the illness made me question my faith in God. How could he do this to me? At one point I stopped believing, but I got more involved in church and now my faith is back." She also switched to a school geared to children with special needs. There she thrived, heading the cheerleading squad and participating in athletics.

Physical and occupational therapy also helped Nancy recover from the strokes. She remembers how Janice Erlandson, RN, one of her long-time nurses, encouraged her to practice her exercises. "She made it into a game. She would curl over with me in her arms and try to get me to use my legs and walk down the hallways so we could practice what we called the 'monster walk.' Every time I saw Janice I asked if she would monster walk with me."

Pat Sedenger, RN, another of Nancy's nurses, says: "After years of coming back and forth to the MGH for care, Nancy is still determined and optimistic. Through the years, she required the services of specialists from many departments, but her care consistently has been coordinated through the Children's Service."

### Nancy takes charge

In the summer after her 18th birthday, Nancy experienced some worsening of her neurological function, and her doctors discussed resuming the chemotherapy. Nancy, however, decided that she no longer wanted to take medications; the side effects were no longer acceptable to her.

"Even when I was younger, I wanted to stop the medicine," says Nancy. "The doctors and my parents wanted me to keep taking it, but they weren't the ones throwing up from the chemotherapy."

Her father, Angelo Digeso, says: "I was a little frightened that she stopped taking the medicine. But I was more concerned with her state of mind. I want to see her happy. If this is what she wants, so be it. I don't make decisions for Nancy; I try to guide her and love her."

Susan Zigelbaum, MSW, Nancy's social worker, explains: "Nancy began coping with her illness as a young child, but she is not a child anymore. She is beginning to deal with her disease as an adult, making more of her own treatment decisions."

Last summer Nancy made another important decision; she requested surgery that might improve her ability to walk and move one of her arms. Damage from the strokes had decreased the strength and flexibility of muscles in her left leg and arm. She wore a brace on her left leg, which she had to push off to the side and then swing forward to walk. By lengthening the muscles behind the ankle and thigh, and splitting the tendons, David Zaleske, MD, pediatric orthopedist, improved the alignment of the foot and knee, allowing Nancy to walk without a brace.

"Deciding whether to intervene, especially with a surgery that has unpredictable outcomes, is always a dilemma in medicine," says Zaleske. "You ask questions: Is it worth it? Will it help or make the situation worse? But quality of care is ultimately determined by the person receiving it, the person living with the illness. It was important to Nancy to try to be independent of the brace, so we operated."

Zaleske performed a similar operation on Nancy's left arm in December. The surgery, followed by ongoing physical and occupational therapy, improved the arm's mobility, and Nancy is overcoming her hesitancy to use that hand in public.

"It was my choice to have surgeries that might help me move a little better so I could start taking more control of my life," she says. "I know I'll never move like other people, but I'm happy with what I've got." ■

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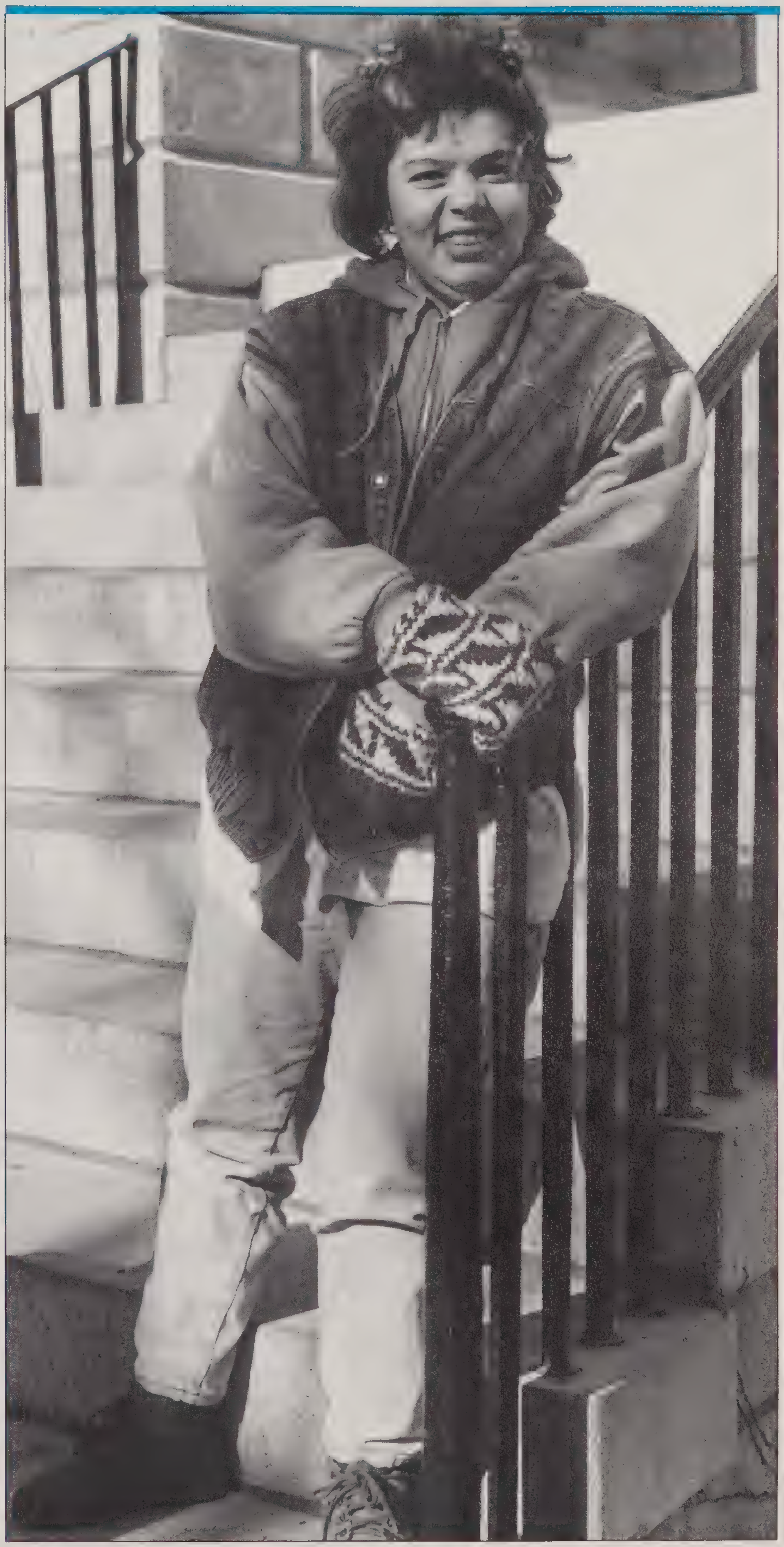


*Nancy Digeso*

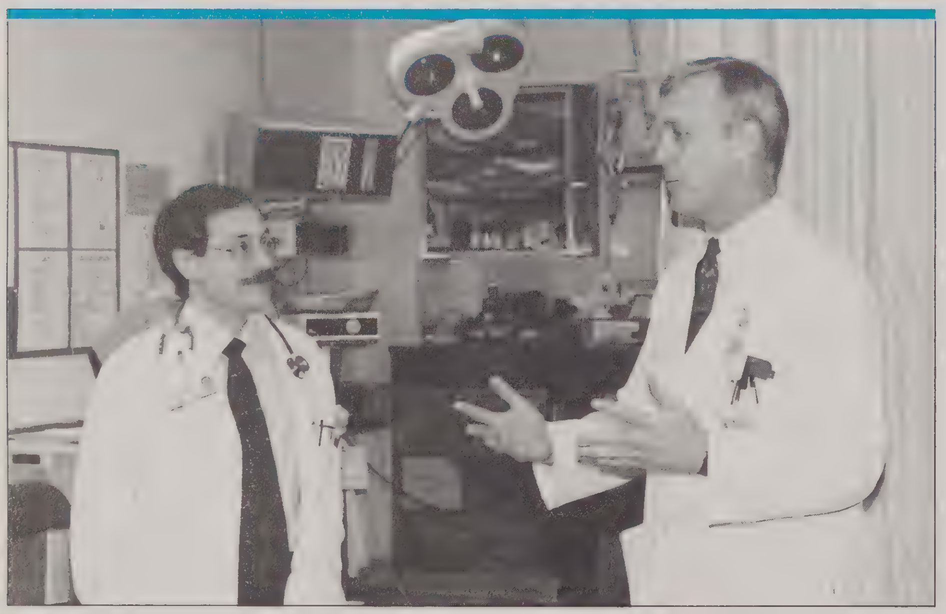
# —Changing times in emergency medicine

*(Continued from Page 1)*

approach to patient care," says Maryfran Hughes, RN, nurse manager. "Patients have become much more sophisticated, much more knowledgeable. They never may have questioned their medical treatment before, but they now feel more empowered to ask what's going on and how treatments will affect them." Because of this new awareness of treatment options, the nurse can be a patient's most valuable resource.

"Nurses play an important role in helping patients and their families through a difficult time," Hughes explains. "Because nurses are able to stay with patients a little longer than the physician, they may notice subtle changes in how patients respond to treatment and are able to intervene when medically necessary.

"Treating the more acutely ill patient is much more emotionally draining for nurses than ever before," she adds. "One of the greatest challenges a nurse faces is delivering care in a way that is comforting, even nurturing, to the most gravely ill patients. And dealing with patients' families can sometimes make that more difficult." Many times a psychiatric nurse clinician, who is specially trained to help families deal with emotionally difficult situations, makes the initial contact with the family.



*In the acute area, Theodore Benzer, MD, emergency medicine specialist (left), consults with Alasdair Conn, MD, chief of Emergency Services.*

The role of the emergency physician is also growing. When Conn arrived at the MGH in 1988, very few attending physicians in the Emergency Department were specialists in emergency medicine. Currently 16 attendings are board-certified in emergency medicine, and there are plans to further increase the staff.

"In response to the changes in emergency medicine, Partners HealthCare System, Inc., [the organization overseeing the affiliation between the MGH and Brigham and Women's Hospital] has committed to further improving the emergency medicine programs at both hospitals," says Conn. Within the next few years the hospitals plan to launch a joint residency program in emergency medicine. Under the direction of Richard Wolfe, MD, of BWH, the program will help position the hospitals for changes in the specialty.

"Most specialty training residencies are focused on diseases of a single organ system — the heart in cardiology; the liver, stomach and intestines in gastroenterology; the lungs in pulmonary," says Wolfe. "Emergency medicine is different. It's based on the time, location and seriousness of an injury. You're a detective; you are given situations and clues, and you need to figure out what's going on. You have to think differently because you have a limited amount of data and time to make a decision."

Emergency medicine is one of the newest specialties. Residency training programs began in the 1970s, and the first specialists were accredited in the early 1980s. "It's always evolving, never static," says Wolfe, who has been in the field for 10 years. "We plan to have 12 residents a year once the program begins. They will rotate through the MGH, BWH, Children's and Mt. Auburn hospitals, with two to four at any one time in each facility."

The emergency residents will not replace the residents from surgery and medicine who regularly rotate through the department as part of their training. Instead the emergency residency program will enhance the other disciplines, allowing more interaction between staff and rounding out the educational experience for all residents.

Research is another focus of emergency medicine. John T. Nagurney, MD, director of research in Emergency Services at the MGH, explains. "We are always looking for the most accurate and efficient way to diagnose and treat our patients, and we are involved in several collaborative research studies with other departments." These departments within the hospital have a need for information that can be obtained from assessments of critically ill patients.

"We hope that data derived from these studies will help develop clinical guidelines on how to diagnose and treat future patients with similar problems," says Nagurney. Some of the studies now underway include examination of patients with closed head trauma, asthma and chest pain.

"Everything we do here is a collaboration," says Conn. "Physicians, nurses, other professionals — we are all intertwined down here. We diagnose and treat the most immediate problems, and the other disciplines take it from there. It all works together."

It is now 4 a.m. on Sunday. Two of the trauma patients are undergoing radiological testing; the other two await their turn. The young asthma patient has finished his treatments and is about to go home. The woman with the benign brain tumor has been admitted to the neurosurgery unit. Her family will be here in a few hours to discuss whether she should have surgery to remove the tumor. All is quiet in the Emergency Department — for now. ■

# New facility is spacious, less intimidating

WITH THE construction of the Blake and Ellison buildings — and a slight name change — Emergency Services has come into the 1990s. For many years located on the first floor of the White Building, the department recently expanded into the Ellison Building. Though the entrance to the new quarters is only 50 feet away from its original entrance, the department has experienced a major transformation.

With this expansion, the new facility doubled its space. Where once there was a confusing network of small rooms, there are now larger, more flexible treatment areas. A specially designed, department-integrated computer system enables staff members to keep track of patients in any one of the department's four main areas: acute, minor, pediatrics and Acute Psychiatry Services.

The acute area consists of the trauma unit and the major multi-purpose unit. With a separate entrance, the trauma unit provides direct access to ambulance crews out of sight of patients in the waiting area. "In the old area, waiting patients would see everyone who came in, including those heading into trauma," says Alasdair Conn, MD, chief of Emergency Services. "We designed the new facility to reduce or eliminate the likelihood of that occurring." In January the hospital began operating a helipad on the roof of the new Blake Building, reducing transport time of very acute patients flown in by helicopter.

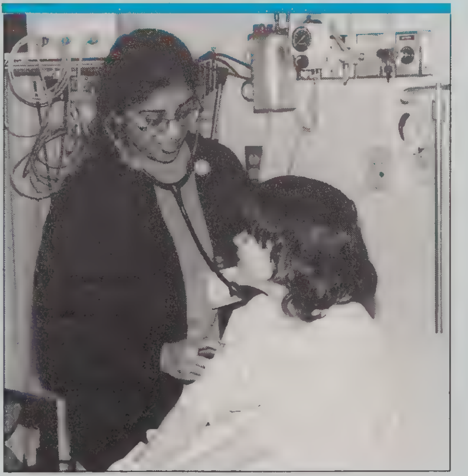
The trauma unit also has a separate four-room facility for cardiac emergency patients and major trauma cases. The unit includes a room with a specially designed ventilation and heating system to accommodate patients suffering from burns or exposure to hazardous materials.

The major multipurpose facility has 16 rooms and a central nursing station. Patients with suspected cardiac problems and those suffering from severe illnesses like pneumonia are treated and observed in this area.

The minor area opened 10 beds in January, during the final stage of the department's move. Patients suffering from viruses, infections, minor injuries, toothaches and other painful ailments are assessed and treated in this section and usually discharged.

Of the 65,000 patients seen in the Emergency Department each year, 7,000 are children. In the old quarters, pediatric patients and their parents had to pass through the entire department to reach their special treatment area. Now the pediatric facility is located away from the main area, and patients and their families are not exposed to other emergency situations. The section contains five patient rooms, each large enough to accommodate patients, caregivers and parents.

> "No one wants to be in an emergency department. The new space is very airy, open and nonintimidating. We want to make our patients feel as comfortable as possible during their time here."
>
> —Alasdair Conn, MD



*Brinda Gupta, MD, Children's Service, treats Jessica Wardwell for dehydration in the new pediatric area of the Emergency Department.*

Previously located on the first floor of the Vincent-Burnham Building, Acute Psychiatric Services (APS) is no newcomer to the Emergency Department. "We have always been a seven-days-a-week, 24-hours-a-day service," says Kathy Sanders, MD, director of APS. "We see close to 600 patients a month, with problems ranging from depression to lapsed medications to suicidal feelings. Our new space — which opened in February — has been designed to accommodate patients who need emergency psychiatric intervention."

APS now has three dedicated rooms to observe patients who require containment. A central staff station is being designed to permit video monitoring of patients in these rooms. Currently patients can choose to have someone sit with them instead of being restrained. Either way, needs can be addressed more effectively in the new environment than was possible previously, according to Sanders. "The older facility was very cramped and could accommodate outpatient treatment only. Inpatient assessments were done in the major multi-purpose area. The new area gives us a single, psychiatry-dedicated area."

Conn notes, "No one wants to be in an emergency department. The new space is very airy, open and nonintimidating. We want to make our patients feel as comfortable as possible during their time here." ■

# Hormone treatment may lead to osteoporosis prevention

THE bone-thinning condition osteoporosis affects more than 20 million Americans and leads to 1.3 million fractures each year. Now MGH researchers may be closer to finding a better way to prevent and someday treat this debilitating problem. A team led by Joel Finkelstein, MD, of the MGH Endocrine Unit, has discovered that daily injections of parathyroid hormone — a substance studied at the hospital for more than 60 years — can prevent the development of osteoporosis in women taking medications that induce an artificial menopause.

Osteoporosis is a gradual loss of tissue within the bones, which causes them to become less dense, weak and brittle. The structure and density of bone tissue are maintained by a constant, balanced process that breaks down old bone and replaces it with new bone. But bones gradually become less dense when breakdown begins to exceed rebuilding after age 35 in women and after 50 in men. Some individuals may be susceptible to losing bone tissue more quickly because of inadequate intake of calcium, certain illnesses or inactivity.

In women, the loss of bone accelerates after menopause with the decline in the natural production of estrogen, which helps to maintain bone mass. During the first years of menopause, some women can lose as much as 20 percent of the sponge-like bone tissue inside the vertebrae, the bones of the spine. If the weakened vertebrae collapse, the spine becomes more compact, leading to a loss of stature. Pain and nerve damage also can occur, and the spine can bow forward, forming the so-called "dowager's hump."

The hard, compact bone tissue that gives strength to the long bones of the arm and leg is also affected by osteoporosis, although somewhat later than spinal bone. Hip fractures, often associated with falls, can cause serious disability; 15 percent of elderly patients with hip fractures die as a result of their injury.

Bones require sufficient levels of calcium to remain strong, and the exchange of calcium between the bones and the bloodstream is controlled by parathyroid hormone (PTH). As a result, PTH has long been of interest to osteoporosis researchers. "Continuous exposure to abnormally high levels of PTH can weaken the skeleton," says Robert M. Neer, MD, director of the MGH Osteoporosis Center, who collaborated on the research. "However, intermittent treatment with low doses of PTH increases the amount and strength of bone."

Early studies with animals showed that PTH injections could cure osteoporosis in rats, but studies in humans who suffer from osteoporosis were less successful. The hormone did increase bone density in the spine but not in the arms and legs. However, says Finkelstein, PTH can prevent or reverse osteoporosis in rats from which the ovaries have been removed, a condition that would mimic a sudden onset of menopause. "We hypothesized that PTH might prevent the development of osteoporosis — as opposed to curing established osteoporosis — in women whose estrogen was reduced to postmenopausal levels by a medical treatment."

**A team led by Joel Finkelstein, MD, of the MGH Endocrine Unit, has discovered that daily injections of parathyroid hormone — a substance studied at the hospital for more than 60 years — can prevent the development of osteoporosis in women taking medications that induce an artificial menopause.**

The researchers looked at a group of women taking nafarelin, a medication that suppresses the natural release of reproductive hormones and causes a temporary menopause in women. One of a group of drugs called gonadotropin-releasing hormone (GnRH) analogs, nafarelin is commonly used to treat endometriosis, a condition in which the tissue that normally lines the uterus grows in abnormal locations, and is also used to treat prostate cancer in men. Both of these conditions require normal levels of the sex hormones estrogen or testosterone, and GnRH analogs block the natural production of these sex hormones.

However, since taking these drugs can cause osteoporosis, treatment of endometriosis is currently limited to six months. (Prostate cancer treatment has no such time limit.) For most patients with endometriosis, painful symptoms eventually return after GnRH analog treatment is discontinued.

In the MGH study, half of the participants received daily doses of nafarelin alone; the other half received both nafarelin and PTH. Over a period of six months, density of the sponge-like bone in the lumbar spine (lower back) actually increased in the women receiving both nafarelin and PTH but decreased in women receiving nafarelin alone. Based on measurements of the forearm, the researchers found no change in the density of compact bone in either group. And there were no serious side effects from the treatment.

"This study shows that PTH can be used to prevent bone loss in these medically induced situations, and we may find that it can prevent it in natural menopause," says Neer. "Not only could this allow people to benefit from GnRH therapy for longer periods of time, but the more we learn about PTH's effects, the greater chance we will have of someday curing osteoporosis."

The researchers note, however, that more studies are required to establish whether PTH will indeed prevent osteoporosis in natural menopause. The hormone is not currently approved for treatment by the FDA and is only available through experimental research studies.

PTH has been studied at the MGH since the 1920s, and researchers in the MGH Endocrine Unit have made many significant discoveries about the hormone and the parathyroid gland in which it is produced. The observation that small, intermittent doses of PTH can increase bone mass was first made at the MGH in 1934, but studies of its possible use in treating or preventing osteoporosis did not become practical until genetic techniques were developed to produce the hormone in large quantities.

Finkelstein notes that no cure currently exists for human osteoporosis. Estrogen replacement is the only FDA-approved way to prevent bone loss in early menopause, but many women reject that approach because of possible unwanted side effects. Other experimental treatments, including a synthetic hormone called calcitonin and a group of drugs called biophosphonates, have been found to prevent bone loss. But whether their risks outweigh their benefits remains uncertain or controversial. While sufficient intake of calcium and vitamin D, along with weight-bearing exercise, are important to maintain bone strength, neither have been proven to prevent osteoporosis on their own.

"Estrogen and current approaches being tested against osteoporosis work by inhibiting the natural breakdown of bone tissue, whereas PTH stimulates the formation of new bone," Finkelstein says. "Because PTH prevents the bone loss associated with estrogen deficiency by this novel mechanism, it may become an important new agent in the fight against osteoporosis." ■

# Center offers coordinated care for thoracic cancer patients

*The news is bad. Your doctor tells you that the symptoms you've been experiencing — coughing, pain in the chest, shortness of breath — are indeed from lung cancer. To get the specialized care you need, you are referred to a medical oncologist. At the appointment several days later, the oncologist says that you will also need to see a surgeon, who may remove the tumor, and a specialist in radiation therapy, who will provide follow-up treatment. Each appointment will require a separate visit to the hospital, an inconvenience that is the last thing you and your family need at this traumatic time.*

That situation, commonly faced by patients at many institutions, is no longer typical at the MGH. Since the opening of the MGH Thoracic Oncology Center last fall, patients with lung cancer and other malignancies of the chest area have had the opportunity for coordinated, multidisciplinary care. In a single visit to the center, patients can meet with many of the specialists who collaborate on their care. The new center is the second such program within the MGH Cancer Center, joining the Comprehensive Breast Health Center.

During an initial visit to the center, patients first meet with Stephanie Macaluso, RN, MSN, a clinical nurse specialist/advanced practice nurse, who takes a complete history and assesses what their special needs might be. "I look at how they are currently functioning, whether there are issues around coping, pain and personal support that should be addressed now or in the future. They also receive an initial assessment from a physical therapist, and as necessary, social workers, dietitians and others can be involved in their care from the first day."

The patients then meet with specialists from medical, surgical and radiation oncology who review each patient's particular needs and develop an individualized treatment plan. Appropriate consultations can be arranged with Respiratory Therapy,

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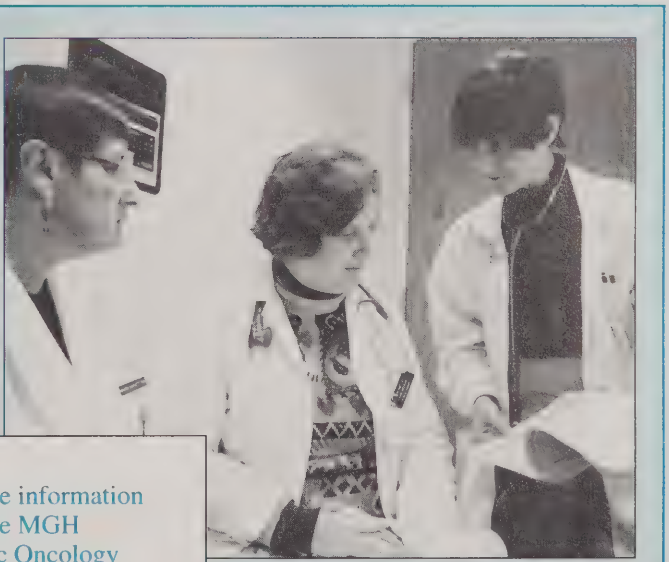


In the Thoracic Oncology Center, Stephanie Macaluso, RN, MSN, (right) clinical nurse specialist, discusses a patient with Manya Barnett, RN (left), and Stella Prevost, PT, physical therapist.

For more information about the MGH Thoracic Oncology Center, including appointments or patient referrals, call 617 724-MTOC (6862).

## — Thoracic oncology

*(Continued from Page 7)*

Speech Pathology, the Pain Center and the Quit Smoking Service. Macaluso and other nurses at the center follow patients through their treatment program, sharing information with other health care providers and making sure that everything stays on track.

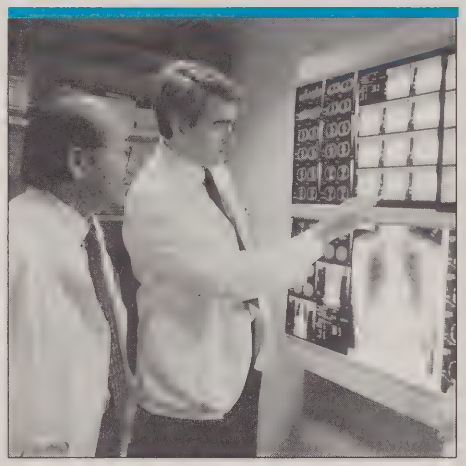
"This approach avoids the need for patients to have multiple appointments on different days with several physicians," says Douglas Mathisen, MD, chief of Thoracic Surgery and a member of the center. "The overall result should be improved patient satisfaction and more efficient care."

Molly Bushman, administrative manager for Surgical Oncology and the MGH Cancer Center explains: "Last year we ran a series of focus groups with cancer patients and their families. They all said the people delivering care were great but that their care felt fragmented. Developing these multidisciplinary patient-focused centers is central to the mission of the MGH Cancer Center."

Thomas Lynch, MD, an MGH medical oncologist who played an instrumental role in establishing the center, adds that important new treatment information is another reason for offering a multidisciplinary treatment approach to lung and other thoracic cancers. "In the last five to ten years, we have learned that adding chemotherapy and radiation to surgical approaches for these diseases can make a difference in long-term survival. This clinic allows us to offer care that is more complete without being overly complicated."

The center's staff also plans to offer support groups for lung cancer patients, who often have to face special issues of their own. "There's blame associated with lung cancer," Lynch says. "Many patients will blame themselves or have blame put on them by family members, society, even their doctors."

Another benefit available to patients at the MGH center is the opportunity to join clinical trials of new treatment methods.



*Noah Choi, MD, left, and Thomas Lynch, MD, review a lung cancer patient's x rays.*

The MGH has recently been chosen as one of four national test sites for a promising chemotherapy drug called CPT-11. Several studies now nearing completion have produced impressive results.

Noah Choi, MD, of the Radiation Oncology Unit, is testing a new approach to treating stage IIIA non-small-cell lung cancer. Standard treatment of this type of cancer — involving surgical removal of as much cancer as possible, followed by radiation, chemotherapy or a combination — produced dismal results. Only 10 to 15 percent of patients survived five years.

In the new approach, radiation and chemotherapy are given more intensively — twice daily with concurrent chemotherapy treatments — before surgery, both to reduce the size of the primary tumor and to destroy distant cancer cells. In the 7-year-old study, which currently includes about 40 patients, five-year survival is about 36 percent. "This program eventually will have to be compared with conventional treatment in a larger group of patients," Choi says. "But our results stand out very well among other studies."

Another study of Choi's is a national study that looks at how much radiation can safely be given to patients with a type of lung cancer that is treated with radiation and drugs. Results so far indicate that the dose of radiation could be increased as much as 30 percent, improving the outcome of standard treatment, which has a local failure rate of 50 to 60 percent.

Lynch notes: "The overall statistics on lung cancer are still quite discouraging. More than 170,000 people will be diagnosed this year, and currently we can expect to cure only 13 percent. But there are certain types of tumor for which we now have much better results. And every refinement we make in treatment, every time we increase the cure rate by a few percentage points, that can make the difference between life and death for thousands of patients." ■

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MGH News

Massachusetts General Hospital, Boston, Massachusetts

June/July 1995

# Winning the race against cystic fibrosis

FOR WORLD-CLASS runners, the Boston Marathon is one of the sport's most visible events, offering an opportunity to enter the history books with a record-breaking performance. For thousands of the less elite, the race is a chance to push their limits, either for a personal best time or simply to finish the grueling course.

But for one group of participants in this year's marathon, the length and the challenge of the race symbolizes the struggles and successes of their own lives. For the third year in a row, a relay team ran the race to raise funds for cystic fibrosis treatment and research at the MGH, and leading the way were 17 adults and children with the disease.

Michael Goddard of Littleton, Mass., a member of the relay team, has been cared for by MGH physician Kon-Taik Khaw, MD, since he was diagnosed with cystic fibrosis as a child. Goddard points out that, while many individuals and teams run the marathon to raise funds to combat illness, it is unusual for a team to feature people affected by the disease.

"Throughout my life exercise has been an important part of staying healthy," he says. "When I first heard that Mary Dunn [another MGH patient] was putting together the relay team three years ago, it seemed a great way to give something back to the folks at MGH who've given us such great care and to support research that may benefit us in the future."

The fact that Goddard and others with cystic fibrosis are living into their adult years — that many are healthy enough to hold jobs, be physically active and contemplate having their own families — is testament to the progress that has been made in treating the most common lethal genetic disease affecting people of European ancestry. And new medications and therapeutic strategies currently being tested at the MGH and elsewhere promise to further improve the outlook for cystic fibrosis patients beyond even the dreams of a few decades ago.

### *Gene defect causes complex problems*

Cystic fibrosis is a genetic disease that appears only if a child inherits two defective copies of the cystic fibrosis gene — one from each parent. The illness affects cells of the epithelium, tissues lining the airways and disgestive system, causing a variety of symptoms. Because the pancreas of people with cystic fibrosis does not produce enzymes needed for proper digestion, children with untreated cystic fibrosis cannot digest nutrients, and they gain little weight. Once the diagnosis is made, the digestive problem can be remedied with oral enzyme replacements. More complex and troublesome is the disease's effect on the lungs.

Epithelial cells lining the bronchial tubes normally produce a thin layer of mucus that coats the lining of the airway, lubricating the surface and trapping germs. In

*(Continued on Page 2)*

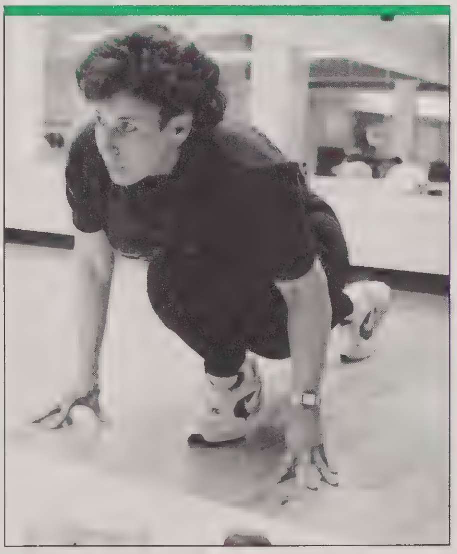
# *Continence Clinic puts patients back in control*

WHEN Carole Bellew of Cambridge had her first child, she expected to have discomfort after the delivery; she expected that the infant would wake up in the middle of the night crying to be fed. But she did not expect that a side effect of her pregnancy would be urinary incontinence, the inability to control the release of urine.

Bellew is one of the 10 million adult Americans who experience incontinence. Most find the problem so embarrassing that they do not even discuss it with their physicians. Others may think incontinence is a normal part of aging and resign themselves to the use of protective pads and garments.

But through proper diagnosis and treatment, many of those with incontinence can find help — or even a cure —

*(Continued on Page 6)*



*After successful treatment in the MGH Continence Clinic, Carole Bellew can once again enjoy her exercise class.*

INSIDE

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# —Winning the race against cystic fibrosis

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cystic fibrosis, the cells produce unusually thick and sticky mucus, which clogs the lungs. While normal mucus can easily be coughed up, along with any trapped germs, the thick mucus of cystic fibrosis is difficult to expel and becomes a source of infection.

"The lungs of patients with cystic fibrosis become colonized with bacteria very early in life," says Allen Lapey, MD, director of the MGH Cystic Fibrosis Center. "When patients are unable to clear their lungs, the bacteria cause infection. The immune system responds, and white blood cells produce inflammation, a process which paradoxically destroys the tissues is designed to heal. Debris then collects in the lungs, leading to more mucus production, more infection—a vicious cycle that eventually causes the lungs to give out."

### *An improving outlook*

As recently as 20 years ago, the outlook for most cystic fibrosis patients was so grim they were not expected to live past the age of 10. Today the life expectancy for a newly diagnosed patient is 30 years and rising.

"When I was diagnosed at 1 year old, my parents were told there was about a 50 percent chance that I'd live past 5," recalls Goddard, who is now 33. "For most of my life I've been a few years ahead of the expected life span. It's certainly encouraging."

*MGH physicians treating cystic fibrosis patients: Kon-Taik Khaw, MD, Allen Lapey, MD, and Patricia Joseph, MD.*

The improvement has come from steady progress in developing ways to help patients keep their lungs clear and reduce the incidence of infection. Special physical therapy techniques, involving vigorous clapping on the back and chest, help patients loosen and expel mucus. More advanced antibiotics can prevent and treat the most common infections. Some of the newest medications are able to thin mucus secretions, and most recently the anti-inflammatory drug ibuprofen has been shown to reduce the damaging effects of the immune system on lung tissue.

"Several years ago the MGH participated in a multicenter trial of the drug prednisone to reduce inflammation in cystic fibrosis," Lapey says. "While the side effects of that powerful drug made its regular use impractical, the study did show that patients taking anti-inflammatory drugs had much slower deterioration of lung function than those taking a placebo. The recent results with ibuprofen appear to give us an effective way of reducing the overzealous immune response that can cause more damage to lung tissue than the original infection."

All of these developments have been focused on relieving symptoms and postponing the lung deterioration that is still inevitable for cystic fibrosis patients. In recent years, however, research has begun offering new options that directly

*Michael Goddard (holding baton) leads the relay team of cystic fibrosis patients and their supporters approaching the Boston Marathon finish line.*

address the disease's mechanism.

A few patients have received lung transplants — new organs that are both undamaged and not subject to the abnormal function of cystic fibrosis. But the continuing shortage of donor organs keeps transplantation out of reach for most patients, and even those who do receive donor lungs must take powerful immunosuppressive drugs to prevent rejection for the rest of their lives.

With the discovery of the cystic fibrosis gene in 1989, researchers began to investigate the possibility of gene therapy, introducing a normal version of the defective gene into the lungs of cystic fibrosis patients. Preliminary studies have had promising results, and a study involving patients at the MGH and New England Medical Center began earlier this year. This study uses a weakened cold virus to temporarily "infect" lung cells with the normal cystic fibrosis gene and if successful could give patients many additional symptom-free years *(see sidebar).*

### *Exploring unknown territory*

The promise of gene therapy is still several years from realization. But as patients like Goddard live longer, they and their physicians continue moving into unknown territory. Khaw, Goddard's physician, explains that while some patients have been able to stay relatively healthy, others are quite ill and struggling with serious problems not seen in children with the disease.

"The better we can understand the adult patient, the better we can control some of the complications that result from the long-term effects of cystic fibrosis on their bodies," Khaw says. "We are now seeing heart disease related to damaged lungs, diabetes related to failure of the pancreas, bone disease and reproductive system abnormalities. As we learn more, we are able to support our patients more efficiently and give them an improved quality of life as well as extended longevity."

New knowledge also is being gained about how cystic fibrosis operates on a molecular level in basic research labs around the country. At the MGH, Dennis Ausiello, MD, chief of the Renal Unit, also heads the Joey O'Donnell Memorial Cystic Fibrosis Research Center, the largest laboratory investigating the disease in the northeastern United States.

Lapey says: "The MGH, which cares for both children and adults, is particularly well positioned to manage a disease like cystic fibrosis that starts in childhood and continues into adulthood. Not only do we have Dr. Patricia Joseph, a specialist in adult pulmonary medicine, on our team, but the nurses, residents and fellows who care for our patients when they are hospitalized are experts in the care of adults with respiratory illness.

"With these new treatment possibilities on the horizon," he continues, "it's more important than ever that we help our patients stay healthy enough to benefit when a new therapy does prove successful. I think within 10 years we really will have this disease under control — I'm very optimistic." ■

## Correcting a genetic mistake

EVERY CELL in the body of a patient with cystic fibrosis carries a defective copy of the cystic fibrosis gene. But it is in the lungs that the disease's most devastating effects occur. So finding a way to introduce a normal version of the mutated gene into the cells lining the respiratory system and inducing that gene to produce a healthy protein are the goals of genetic therapy for cystic fibrosis.

The approach currently being tested at the MGH and New England Medical Center uses an engineered version of an adenovirus, a common cold virus, to which a normal cystic fibrosis gene has been added. Developed by Genzyme Corp., the virus vector takes advantage of the natural ability of adenovirus to infect cells lining the respiratory system. While the vector can introduce the normal gene into cells, it is not able to reproduce itself and cause cold symptoms.

Because the current study is designed to test the safety of the treatment, the first phase involves delivering the vector to only a small area of the lungs of participating patients via a bronchoscope, a slender tubular instrument. If there are no negative side effects, the study will proceed to a second phase, in which patients will receive the vector by aerosol — a fine mist that can be inhaled to deliver the vector to the entire surface of the lungs.

"We need to start with bronchoscopic administration to a small area because of the possibility that the virus might regain its reproductive ability or produce an inflammatory reaction in the lungs," says Patricia Joseph, MD, pulmonary disease specialist, who is administering the therapy to MGH study participants.

Bronchoscopy is an invasive procedure requiring sedation, and early studies indicate that the DNA introduced is active for only four to six weeks. Repeated bronchoscopies would be impractical and disruptive for patients. Joseph notes that aerosol administration, which patients could comfortably receive in their doctors' offices, will probably be the preferred method.

"The aerosol portion of the study is really the most innovative aspect of this project; it will be the first approved aerosol administration of any gene vector in North America," she says. "Tissue culture studies suggest that we can make a real difference in how the respiratory lining behaves by infecting only 5 to 10 percent of cells with the normal gene."

The safety study will enroll a total of 40 patients — 20 at each hospital — and should last a year. If it is successful, the next step would be a larger-scale study to examine how well the therapy actually works in relieving cystic fibrosis symptoms. ■

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PHOTOGRAPHS: Page 1,2 (upper), 4,6,8 Susan McGreevey; page 2 (lower) courtesy of Michael Goddard. Illustration page 5 Arch MacInnes.

# Proteins, genes and molecular machines

IN ONE OF history's largest scientific endeavors, scientists around the world are working to decode the millions of genes that make up human DNA. When the Human Genome Project is complete and every human gene is identified along with its chemical sequence, then things will *really* get complicated. Each gene contains instructions required to make a protein, and proteins are what carry out the business of life. The way proteins go about this business, however, is far from simple.

Proteins operate by communicating with other proteins, which communicate with still other proteins in lengthy and complex cascades. To understand fully how a particular gene functions — or malfunctions when it is mutated — scientists need to unravel the intricate web of interactions that the protein created by that gene makes with its partners. Roger Brent, PhD, of the MGH Department of Molecular Biology, and his colleagues study how proteins interact with each other, with particular emphasis on proteins that control the proliferation of cells.

"Let's say a cell needs to start growing," Brent explains. "What happens very typically is that a protein called a receptor, embedded in the outer surface of the cell, receives a signal from another protein called a growth factor. Part of the receptor passes through the cell membrane to the interior of the cell. When the growth factor and the receptor 'talk to each other,' the receptor then interacts with another protein inside the cell, altering it in some way. That leads to changes in still more proteins that eventually turn on genes the cell needs to grow and divide."

### *Detecting protein interactions*

When scientists identify a protein, they traditionally study it in isolation, figuring out its exact sequence of amino acids and the three-dimensional structure of the molecule, finding the gene that encodes it, and studying its action in simple, test-tube systems. In their search for new ways to study groups of proteins that interact together, Brent and his colleagues have developed ways to build tiny "machines" out of bits of protein and DNA, machines that take advantage of the natural functions of these molecules.

The sequence of chemicals in a double-stranded DNA molecule corresponds to a code for constructing proteins. However, not every portion of the DNA is a protein recipe or gene. Some segments carry instructions that tell the cell whether or not to make a protein encoded further along the DNA strand. It usually is necessary that an instruction site be turned on by a special protein known as an activator for a gene to be read or transcribed.

"The people working in my lab figure out how to use the transcription of genes, a process we understand pretty well, to learn more about processes we don't understand, like the interactions between proteins," says Brent.

The basic concept, developed by Brent and his colleagues along with workers in other labs, shows whether two proteins interact. One protein, called the bait, is fused to the instruction site of a strand of yeast DNA that contains what is called a reporter gene. (Yeast cells are used for many basic science experiments because they are similar to those of higher animals.) Another protein, called the prey, is fused to an activation protein that could turn on the DNA's instruction site.

Then the prey proteins are introduced into yeast cells that have bait proteins fused to their DNA. If the bait and prey proteins interact, the activation protein

*Roger Brent, PhD (right), and graduate student Barak Cohen examine a plate of yeast cultures for evidence of protein interactions.*

attached to the prey is able to turn on the DNA's instruction site. That leads to transcription of the reporter gene, which leads to production of a clearly recognizable signal. Depending on the reporter gene used, the yeast cells may turn a special color or be able to grow in a particular environment *(see diagram).*

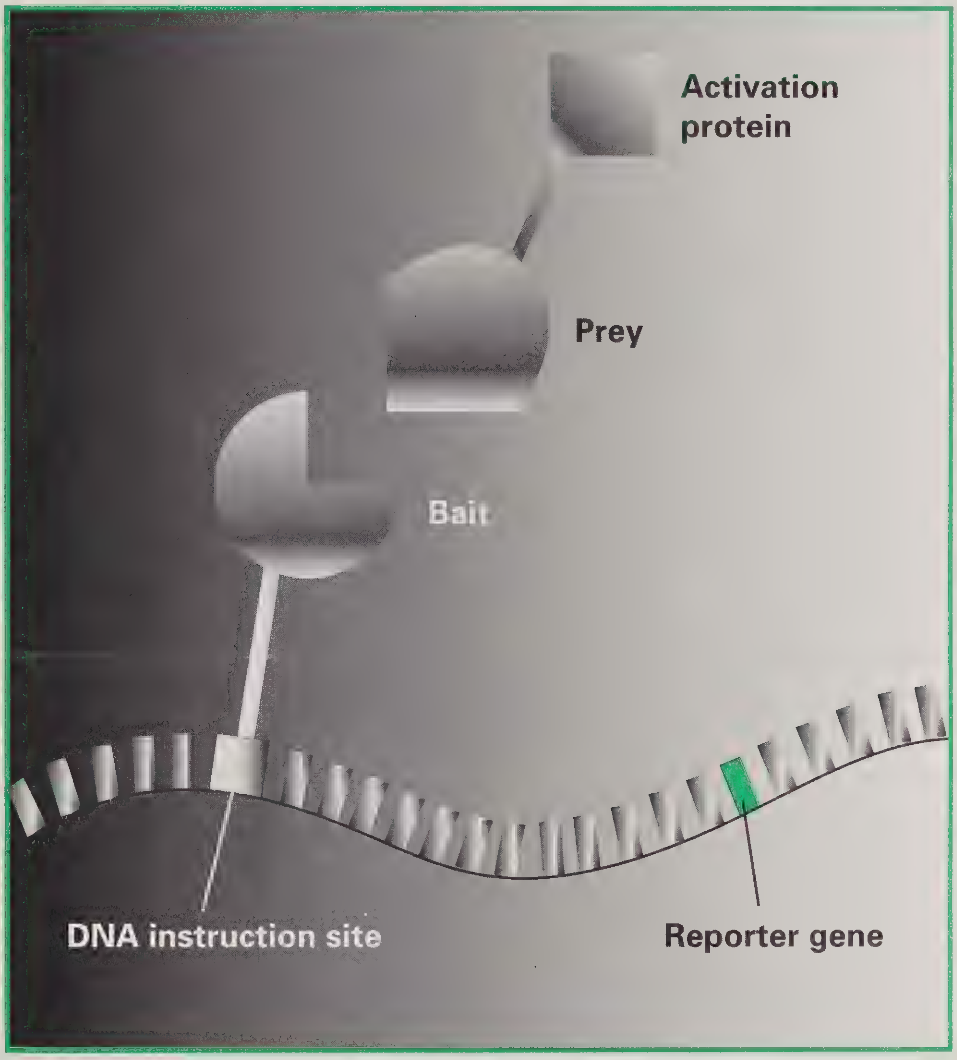
Their technique, called the interaction trap, has been adopted by labs across the country that study connections between proteins. Brent and his colleagues have both improved the original method and used it in their own protein studies, which are producing important results. Russell Finley, PhD, developed a way to test for interactions between several proteins at the same time, and in a study published earlier this year was able to show that three cell-growth proteins interacted in a more complex way than had been previously expected.

"He not only showed that protein A interacted with protein B and protein C, but also that proteins B and C interacted with each other," says Brent. "That kind of information allows us to develop maps of the networks of connections proteins make with each other. Analyzing the patterns made by these networks has the potential to give us important, unexpected information about how the proteins behave in normal situations and in disease."

### *Concrete applications of abstract work*

The highly abstract work of analyzing protein network patterns could someday have very concrete applications. When researchers identify a gene associated with an illness, they are still a long way from turning that discovery into an improved treatment or cure. They need to understand how mutation of that gene, and subsequently of the protein it encodes, leads to a breakdown in normal functioning. Finley has theorized that showing a difference between the way a normal protein and the disease-associated form interact with other proteins may be able to identify which proteins are involved in the disease process, information that could have important clinical application.

For example, mutations in several proteins involved in controlling cell growth have been implicated in the development of certain cancers. Understanding the network of connections made by those proteins could lead to new types of cancer treatment. "If we could have something that recognized the cancer-associated form of a protein and could block its interaction with other proteins and could do that inside a living cell, we'd be able to stop that cell from proliferating and stop the cancer," Brent says.



*If the bait and prey proteins interact with each other, the activation protein will turn on the instruction site on the DNA, resulting in transcription of the reporter gene, which produces a recognizable signal.*

And another tool developed by the MGH team may be able to do just that. In cooperation with researchers from Genetics Institute, Brent's team has developed small synthetic proteins, made by fusing a string of amino acids called a peptide to a larger protein that holds both ends of the peptide and displays it to the cellular environment. The team has developed hundreds of millions of these proteins, each with a slightly different peptide shape and sequence, and has identified ones that interact with natural proteins.

In their ability to very specifically recognize a particular form of a protein, these synthetic proteins — which are called peptide aptamers — are similar to monoclonal antibodies, specialized immune system cells that have many scientific and medical uses. But while monoclonal antibodies identify and bind to proteins on the outside of cells, aptamers are capable of functioning inside cells. A monoclonal antibody can zero in on a particular type of cell and suppress its activity or deliver a drug. The aptamers theoretically could move inside the cell and block a specific protein interaction involved in a disease.

"As biologists working with cells in a laboratory, we can always get a piece of DNA into a cell to make a certain protein. But a physician treating a patient with cancer or a genetic disease cannot do that," Brent says. "We know that these peptides can manipulate protein interactions, but we have a lot of questions about how or whether they will work in animals and eventually in people.

"Finding those answers could take 10 years or more. But if our theory is right, we might develop new treatments for cancer that have no effect on normal cells but are as effective against tumors as antibiotics are against infection." ■

# —Continence Clinic puts patients back in control

*(Continued from Page 1)*

often without surgery. The MGH Urology Unit offers a Continence Clinic emphasizing conservative, nonsurgical approaches to regaining bladder control.

Elizabeth Montgomery, RN, neurourology nurse clinician, runs the clinic. She explains that urinary incontinence can affect people at all stages of life. "While the problem does occur most frequently in older individuals, many young women have trouble after giving birth," she says. "Men can become incontinent because of benign prostate disorders or after prostate cancer surgery."

Scott McDougal, MD, chief of Urology, adds: "Incontinence can be terribly disruptive of people's lives, to the point that some never leave their homes. But there are a lot of ways we can help patients, and most of these methods do not require surgery."

*Elizabeth Montgomery, RN, helps patients use a variety of techniques to regain bladder control.*

### *A worsening problem*

Although Bellew's initial experience with incontinence disappeared soon after she had her first child at age 39, the problem recurred and worsened when she had her second child several years later.

"When you're pregnant, you always have to go anyway. So at first I didn't think much about it," she says. "But when I took my sons to the park and tried to run with them on the field, I couldn't do it; I leaked. Then I went back to the exercise class I'd been taking for 20 years, and after a few minutes of warmup we started doing jumping jacks. That was it. I couldn't continue."

Bellew saw a urologist at a local hospital and was not pleased with the experience. "He examined me, gave me some tests, and told me I had a serious problem. He said that my muscles had become lax, and the only options he offered me were surgical. But with two small children, I couldn't take the time off that surgery would require."

Deciding to seek a second opinion, Bellew consulted a urologist at the MGH. "This doctor told me that, compared to a lot of other patients, I didn't have a major problem and thought we should wait and see before trying surgery."

> **"Incontinence can be terribly disruptive of people's lives, to the point that some never leave their homes."**
>
> **—Scott McDougal, MD**

The doctor also suggested that Bellew work with Montgomery at the Continence Clinic to strengthen her pelvic muscles. "That's exactly what I was looking for, a way to solve the problem with my own body before resorting to surgery," Bellew says.

Like Bellew, some patients become incontinent because of a weakening of important pelvic muscles — such as the sphincters that release urine or the muscles in the bladder itself. The muscles can be strengthened through exercise, but doing the exercises properly sometimes can be difficult.

Montgomery explains that some patients may not be able to identify the correct muscles or perceive when they are contracting them. "We have two techniques that can help in these cases," she says. "Biofeedback, which translates a physical action like tightening a specific muscle into a visible or audible signal, can confirm when patients are contracting the correct muscles. When that doesn't work, equipment to directly stimulate the appropriate muscles can start the strengthening process."

Both biofeedback and muscle stimulation were part of the program Bellew followed. "When I first started working with Liz, my muscle had no ability to contract; it was virtually gone," she recalls. "It was amazing to sit in those weekly sessions and feel the muscle start to come back. Once I became consciously aware of it, I knew just what I needed to do."

### *Several types of incontinence*

The type of incontinence experienced by Bellew, when urine is lost during exercise or certain motions, like sneezing or laughing, is called stress incontinence. Patients may also have urge incontinence, which is a loss of urine as soon as they feel they need to go to the bathroom, or overflow incontinence, in which they lose small amounts of urine during the day and night and never feel that they can completely empty their bladders.

Neurological disorders also can affect the ability to sense bladder fullness or control urination, and people who are immobilized because of illness or injury simply may not be able to get to the bathroom in time.

For many of these patients behavioral techniques, such as restricting the amount of fluids consumed and urinating at scheduled intervals, can help avoid accidents. Appropriate medication can either stimulate or relax muscles or treat infections. In certain cases surgery may be required to correct a structural problem.

Montgomery adds that none of these approaches works overnight; patience and motivation are required for success. And to help patients cope with the impact incontinence may have had on their lives, the MGH clinic staff also addresses psychological, social and even financial issues. “We provide the support and encouragement patients need to resume an active life,” she says.

Bellew says that she was particularly pleased to be involved in the choice of her own treatment plan. Her incontinence is now under control after eight weekly sessions at the Continence Clinic. “It's also really important for women to be aware of this problem — my gynecologist never told me about the possibility of incontinence after pregnancy — so they won't be caught off guard if it does occur.

“Incontinence is not something people like to talk about,” Bellew adds. “I discussed it in my exercise class, and the instructor told me she knows several women with the same problem who didn't know what to do. But with the right information and help from people like Liz and the rest of the MGH staff, we can be in control once again.” ■

### For more information

Women or men of any age who would like information about the MGH Continence Clinic should call (617) 726-4530.

# Chabner named director of Hematology and Oncology

BRUCE CHABNER, MD, an international leader in developing new treatments for cancer, has been named director of the Division of Hematology and Oncology in the MGH Medical Service and clinical director of the MGH Cancer Center. He is the former director of the Division of Cancer Treatment at the National Cancer Institute.

During his 26-year career at the NCI, Chabner played a critical role in developing and determining the safe use of many of the currently useful chemotherapy agents. He and his colleagues also have helped define how tumors become resistant to certain drugs. In his role as director of Cancer Treatment, he oversaw the funding of major research programs across the country and has been a leading advocate for speeding the drug-approval process for diseases such as cancer and AIDS.

John Potts, MD, chief of the Medical Service, states: “We are delighted to have recruited Dr. Chabner after a several-year search for an outstanding leader to head the division. He combines great skills as physician and clinical investigator with considerable national stature as a spokesman on issues relating to both patient care and clinical research.”

> “We realize now that probably the most effective way of dealing with cancer is to determine who is most likely to develop cancer in the future and then find ways to prevent a tumor's development or to detect it early enough for successful treatment.”

Kurt Isselbacher, MD, director of the MGH Cancer Center calls Chabner “one of this country's most outstanding oncologists. The MGH is very fortunate to have recruited him. Among his objectives here will be developing new, more effective and less toxic anticancer agents.”

Discussing his new position, Chabner cites both the MGH's outstanding patient care record and its world leadership as a center for cancer research. “The MGH has a reputation as a hospital where the physicians, nurses and staff are personally committed to their patients' care. Even the physicians who are deeply involved with research have not lost the patient-centered perspective that is so crucial. It's an extraordinary institution, and I've been very impressed with everyone I've met here.

“We're also in the center of the best scientific environment in the world — with MIT across the river and Harvard Medical School and the other teaching hospitals across town. The resources we can draw on to develop better ways of treating patients with cancer are unmatched anywhere.”

Over the past 20 years, Chabner says, research advances have led to steady progress in improving the outlook for patients with cancer. “While improvement has not been by leaps and bounds, there have been significant changes. For example, in recent years we've started to see a drop in the death

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rate from breast cancer, probably reflecting increased use of mammography and the addition of radiation and chemotherapy to surgical treatment."

The discoveries made by today's researchers promise even greater improvements. "Past cancer treatment depended on drugs that took a relatively crude and unsophisticated approach to stopping DNA synthesis," he explains. "With the new understanding of how the body's chemical signals control cell growth, we hope to develop compounds that are less toxic and are specifically targeted to cancer cells."

Cancer genetics also will become a more powerful tool in the coming years, he adds. "We realize now that probably the most effective way of dealing with cancer is to determine who is most likely to develop cancer in the future and then find ways to prevent a tumor's development or to detect it early enough for successful treatment."

Among the cancer drugs Chabner helped to develop are methotrexate, a standard agent used in lymphoma therapy, and taxol, which has shown promising results in treating ovarian cancer. "I was fortunate enough to get involved in the early history of treating cancer with drugs and was particularly interested in how the drugs worked and what factors determined their effectiveness or toxicity," he explains.

Chabner has long been concerned with assuring the safe use of all cancer drugs, a topic that has received considerable media attention recently. "Close cooperation between oncologists and pharmacists is essential when dealing with drugs that can be very toxic, and the MGH pharmacy is one of the best I've ever seen," he says. "Our staffs have been investigating ways to improve safeguards against improper dosages for some time, and have already taken steps to standardize all protocols [procedures followed in a research study]."

A graduate of Harvard Medical School, Chabner served as an intern and junior resident at Brigham and Women's Hospital. He completed his senior residency in medicine at Yale-New Haven Medical Center and received oncology training at NCI. He has been appointed a professor of Medicine at Harvard Medical School. ■

*Bruce Chabner, MD*

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MGH News

Massachusetts General Hospital, Boston, Massachusetts

September / October 1995

# Life-saving transplant is a family affair

JENNIFER QUERUSIO is a fighter. As a small child she beat the odds and survived a bout of cancer. Now 32 years old, Querusio is surmounting a life-threatening lung disease through the expertise of the lung transplant team at the MGH and some very special support from her family.

On June 5, Querusio's sister and brother each donated a lobe of one of their lungs to their sister, making Querusio the first person in New England to receive a lung transplant from living donors, a technique pioneered two years ago in California. The success of that procedure has turned Querusio's life around and demonstrated a new option for people needing a lung transplant.

***A diagnostic detour***

When Querusio began having difficulty breathing in her mid-20s, her family doctor diagnosed asthma and prescribed

*(Continued on Page 2)*

*To help save the life of Jennifer Querusio (center), her sister Maryann Mills and brother Chuck Marshall each donated a lung lobe for transplantation.*

# *Women's Health Associates fosters sharing information, decisions*

IN 1985 Sally Wyatt, a recently divorced Boston area woman in her mid-40s, approached her family physician with deep-rooted concerns about her health. Both her mother and sister had suffered with breast cancer, and she knew this family history placed her at greater risk for developing the disease. Wyatt was unsure what measures she could and should take to protect herself.

The physician advised her to have both breasts removed as a preventive measure, and a second opinion from a New York City doctor confirmed the recommendation. During a follow-up visit, her physician stressed that if she did not undergo the prescribed procedure, he could not in good conscience continue to provide her medical care.

The choice was clear: Wyatt would have to undergo a double radical mastectomy or find a new doctor. She chose the latter.

***Women's Health Associates at MGH***

Eventually Wyatt found her way to Karen Carlson, MD, at the newly opened Women's Health Associates at the MGH. Here she was able to exchange a seemingly black-and-white approach to her health for a rainbow of information and options.

Following a complete physical examination, Carlson and William Wood, MD, then chief of Surgical Oncology at the MGH, informed their newest patient that her risk for developing breast cancer was 30 to 40 percent. Together Wyatt and her physicians discussed several possible courses of treatment and the related risks.

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# —Life-saving transplant is a family affair

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standard medication. But the treatment did little good, and her condition worsened, particularly with her first two pregnancies. After becoming pregnant with her third child, the Somerville resident consulted pulmonary specialist Jonathan Strongin, MD, of Whidden Hospital. He discovered the original diagnosis was wrong: Querusio had a much more serious condition called pulmonary fibrosis.

In pulmonary fibrosis, the cause of which is unknown, lung tissue becomes scarred and as a result shrinks and stiffens, compromising its ability to deliver oxygen to the bloodstream. While treatment with steroids and other drugs can slow the process for some patients, in others the disease progressively worsens, threatening their lives. In Querusio's case, medication did not help. She began to require supplemental oxygen, and her activities became greatly restricted.

"I'm the type who always likes to be in control," she recalls, "and I had to learn to let go of that. I had three small children, and I couldn't even make dinner for them; family members and friends had to help out. I needed to receive more and more oxygen. I had no life."

When it became clear that medical treatment was not helping and that Querusio and her family were ready to explore other options, Strongin referred her to MGH pulmonary specialist David Kanarek, MD, who arranged her evaluation for a lung transplant. In December she was accepted and placed on the list of MGH patients waiting for a donor lung.

### *A lengthy, risky wait*

Lung transplantation is becoming widely accepted as a treatment for several end-stage lung diseases, but finding a suitable donor lung can be more difficult than acquiring any other organ, explains Leo Ginns, MD, medical director of the MGH Lung Transplant Program. "Most organ donors become donors because they've had some kind of traumatic injury, and any kind of trauma can cause lung injury, potentially including infection."

Lungs can also be damaged when a patient is put on a ventilator, a common occurrence for someone who becomes an organ donor. In addition, factors like smoking or exposure to air-borne pollutants, which have little effect on the quality of other solid organs, can make lungs unsuitable for transplantation."

Because of these limitations, as well as the continuing donor scarcity that is particularly acute in New England, most potential MGH lung transplant recipients face a wait of up to two years for a cadaver donation. That news was particularly discouraging for Querusio because patients with her condition can face rapidly worsening health. The chance that she would live long enough to receive a standard transplant was very slim indeed.

### *A new option*

But Querusio had a piece of luck: The MGH and the other hospitals comprising the Massachusetts Consortium for Lung Transplantation (MCLT) had begun examining the possibility of transplanting lobes from the lungs of living-related donors. So when Querusio's husband asked Ginns if there were any way a loved one could give her a lung, the answer was a qualified yes.

"Dr. Ginns said that they hadn't done such a transplant yet, but that it had been done at a few other hospitals and was a possibility we could talk over. But I knew I wasn't going to make it any other way," Querusio says. "That night I spoke with my brothers and sisters and asked if they'd consider donating. They all said yes, there was no hesitation at all."

All four of Querusio's siblings were evaluated, and three — her sister Maryann Mills and her brothers Chuck and Chris Marshall — were found to be appropriate matches. Her other sister Lisa had an incompatible blood type. After meticulous physical examinations to ensure that donation would pose no unusual health risks, as well as psychological counseling sessions to ensure that no one felt undue pressure to donate, Mills and Chuck Marshall were selected to be the donors, with Chris as a backup.

The three simultaneous operations were performed by John Wain, MD, surgical director of the MGH Lung Transplant Program, along with Cameron Wright, MD; Daniel Ryan, MD — both MGH thoracic surgeons — and Douglas Mathiesen, MD, MGH chief of thoracic surgery. Also participating were MCLT surgeons Craig Lillehei, MD, of Children's Hospital; Steven Mentzer, MD, of Brigham and Women's Hospital; and Joseph LoCicero, MD, of Deaconess Hospital.

The donors recovered rapidly and went home in a few days. Querusio had a few minor setbacks, but within a week she

*Jennifer Querusio answers questions at a news conference.*

began to feel the results of the operation.

"I actually felt nervous because I was using less and less oxygen. I was used to such a constant blast," she says. "But I was up and around and out of intensive care faster than anyone told me to expect." Three weeks after the operation, Querusio went home, and since then her condition has steadily improved.

"There really are no restrictions on her activities," says Ginns. "She can do anything she feels capable of. As she gets better conditioned, she'll feel capable of doing more and more."

Wain adds: "Of the patients who receive lung transplants here at the MGH, almost 90 percent are alive a year later. I hope and believe with every part of me that she will be one of that 90 percent and will continue in good health for the future."

### *An unbelievable change*

Today Querusio says that her breathing is "9 on a scale of 1 to 10. Except for the effects of the anti-rejection drugs, I feel like none of it — the illness, the operation — ever happened. I can't believe the things I can do now."

Her donors, both of whom had smooth recoveries, have returned to full activity and are proud and grateful to have been able to help their sister. "We saw Jennifer go from a healthy, active woman to becoming completely debilitated," Mills says. "We were so happy that she had another option and that we could help. Would I do it again? Absolutely — in a minute!" ■

## A unique approach

THE OPERATION in which Jennifer Querusio received two lung lobes — one from her brother and one from her sister — was not only the first such surgery in New England, it also was unique among the approximately 30 living-related donor lobe transplants accomplished in this country.

John Wain, MD, surgical director of the MGH Lung Transplant Program, explains that the operation typically involves completely removing both lungs and replacing each with the lower lobe from a donor. (The right lung has three lobes, the upper, middle and lower; the left lung has two lobes.) While Querusio's left lung was removed and replaced with her brother's lower lobe, on the right side, only the lower lobe was removed and replaced with her sister's lobe *(see diagram).*

"In simple lobe transplantation, the air passages and blood vessels in the lobe are quite a bit smaller than the structures to which they are attached," Wain says. "Attaching a lower lobe to a middle lobe can make the operation easier.

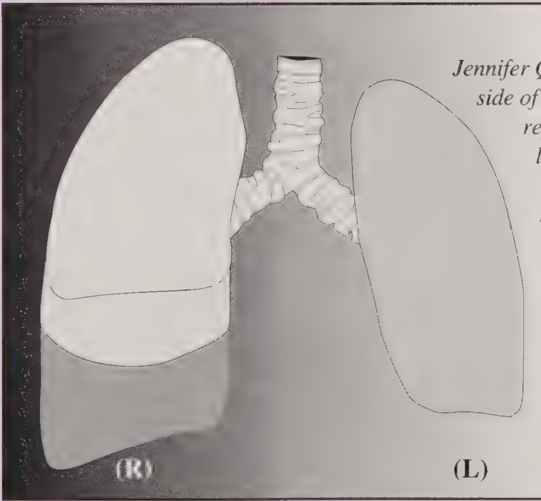
"Giving her extra lung tissue to live on while we implanted the other lobe provided a second advantage," he continues. "In all other living-related lobe transplants, patients have been placed on cardiopulmonary bypass [a machine that takes over the function of heart and lungs], which carries risks like bleeding, infection and stroke. By retaining part of her original lung, we could avoid the bypass machine."

The MGH team has performed 40 cadaver lung transplants since the first operation was done in 1990. Although other centers do more transplants, the MGH has an impressive success rate. The hospital's one-year survival rate is 86 percent, and about 75 percent at two and three years, compared to an average national survival rate of about 65 percent at one year and close to 50 percent at two and three years.

Among reasons for this success, says Wain, is the team's selectivity in choosing organs. "We actually care for a lot of high-risk patients — more than 40 percent could be considered high risk. But we try to be very meticulous about donors in order to give our patients the best possible lungs."

To further improve the success of all lung transplants, researchers at the MGH and elsewhere are pursuing several paths of investigation. "This operation actually illustrated a couple of approaches that might be applied more widely," Wain says. "Our success in leaving part of one native lung in place and transplanting just the single lobe means that we may be able to take that approach when part of a cadaveric donor's lung is damaged but one lobe is in good shape.

"We also tried a new technique of administering nitric oxide gas, which may reduce deterioration in the donor lung, to both donors and recipient. We saw no adverse effects in this operation, and if future research confirms a positive effect, it may prove a way to optimize organ preservation from all donors," Wain adds. ■



*Jennifer Querusio's left lung (right side of diagram) was completely replaced with her brother's lower left lobe, which was almost as large as the removed lung. However, on the right, only Jennifer's lower lobe was removed and replaced with her sister's lower lobe. This approach simplified the surgery and eliminated the need to use a heart-lung bypass machine.*

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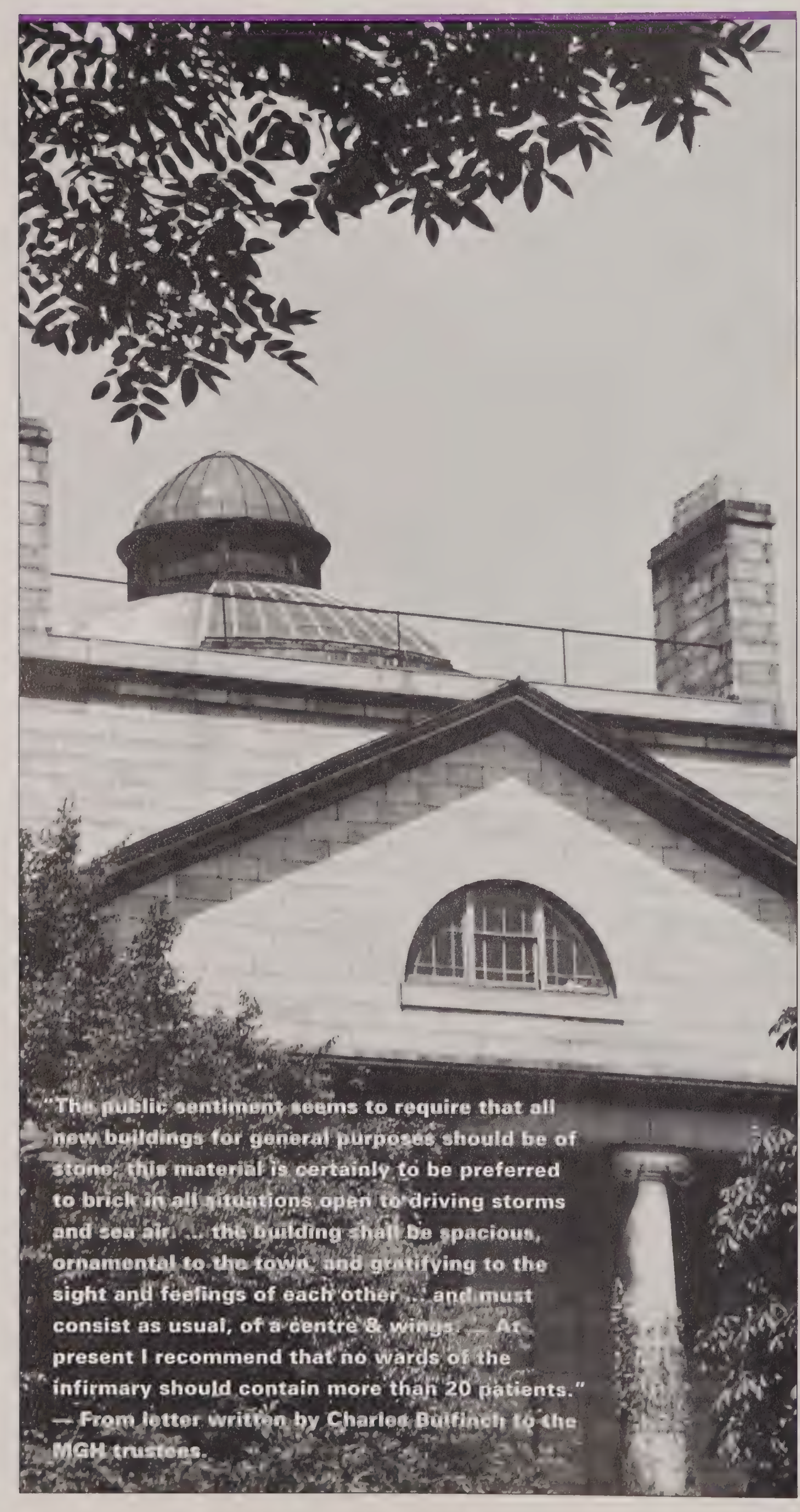
# Times, they are a changin': a brief look at the



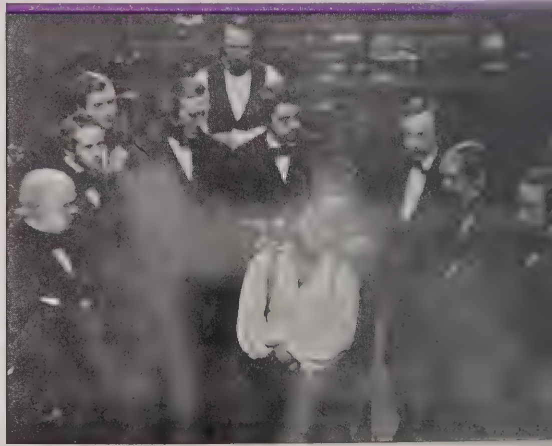
"The public sentiment seems to require that all new buildings for general purposes should be of stone; this material is certainly to be preferred to brick in all situations open to driving storms and sea air. ... the building shall be spacious, ornamental to the town, and gratifying to the sight and feelings of each other ... and must consist as usual, of a centre & wings. ... At present I recommend that no wards of the infirmary should contain more than 20 patients." — From letter written by Charles Bulfinch to the MGH trustees.

A 174-YEAR tradition came to an end in April when the MGH Inpatient Psychiatry Service moved from the Bulfinch Building to the new Blake Building. For the first time since the hospital opened on the shores of the Charles River in 1821, no inpatients are housed in the building that has symbolized the MGH throughout its history.

*In the beginning . . .*

In December 1816, five years after the MGH was chartered, Bostonians were still raising money to build the hospital. After a successful weeklong fund-raising campaign, which brought in almost $100,000, the trustees decided that it was time to obtain professional architectural advice. They turned to Charles Bulfinch, a prominent local architect who had designed the Massachusetts State House. Bulfinch was asked to visit the country's two existing hospitals in New York and Philadelphia, as well as various asylums in both those cities and to report back his impressions and ideas for such a hospital in Boston.

Ground was broken for the hospital in 1818. The building was one of the first American institutions of its type to have interior plumbing. The trustees requested



*"Gentlemen, this is no humbug," said MGH co-founder John C. Warren after removing a tumor from the neck of patient Gilbert Abbott on Oct. 16, 1846. In the first demonstration of anesthesia in surgery, the patient felt no pain, suffered no aftereffects from the gas and recovered fully. The operating theater in which the historic operation took place is now called the Ether Dome. (This image actually shows a re-creation of the ether demonstration. No photographs were taken of the original operation.)*

# ulfinch Building

*During the Civil and Spanish American wars, medical tents were erected on the Bulfinch Lawn to admit the overflow of patients treated for wounds suffered in battle.*

that the hospital have some of the "comforts of home," so a library, kitchen, laundry and washroom were included in the design. Housing was also provided for the hospital's resident physician and his family. Three years after construction began, the hospital's first patient was admitted.

### *The advent of anesthesia*

In the early 1800s the practice of medicine and surgery within hospitals was new. Some of the interventions used, when compared with modern standards, now seem barbaric. Surgical operations had to be performed at lightning speed because patients were awake throughout the procedure.

The events of Oct. 16, 1846, changed that forever. On that day in the Bulfinch operating theater, dentist William Morton demonstrated the relief that inhalation of ether provided to patients undergoing surgery. The patient, Gilbert Abbott, needed a tumor on his neck removed. After administering ether to Abbott, Morton handed him over to surgeon and hospital co-founder John Collins Warren, who performed the surgery without a hitch. The patient reported no pain, and the practice of anesthesiology was born.

### *Growing pains*

By 1843 the hospital's patient population had grown too large to accommodate comfortably in the Bulfinch Building. Often, it was necessary to erect medical tents on the hospital's lawn to house the overflow. Two 50-foot-long wings were added to both sides of the facility. Staff was expanded as well, from 12 to 24 physicians and surgeons. In 1872 an apothecary, or pharmacy, was built on the ground floor, and a year later, a new entrance was cut on the north side of the east wing, providing direct access into the "accident room."

In the ensuing years, Bulfinch began to lose some of its long-time tenants. Rooms on the second and third floors that housed the resident physician and his family were converted to offices when the Resident Physician's House was built in 1891. The operating theater, now called the Ether Dome, was subsequently used as a patient ward, a storage area, a nursing dormitory and eventually a lecture hall. A new kitchen was added, as was a much-needed children's ward. The medical library was moved and its space was converted to a patient ward. Modernization added laboratories, elevators and fireproofing.

By the late 1930s the Mallinckrodt Research Unit, where patients participating in research studies were admitted, and the Inpatient Psychiatry Service were in full operation on the first and third floors, respectively. By now, Bulfinch's patient capacity was well over 200.

### *The end of an era*

By 1977 the Bulfinch Building was more than 150 years old and beginning to show its age. Because the facility could not accommodate modern equipment, its medical beds were moved to the Bigelow Building. Inpatient Psychiatry remained as the only patient unit in the building, which also housed administrative and outpatient offices as well as laboratories and research areas.

The Bulfinch Building and the Ether Dome are national historic landmarks. Although changes may occur within the building's walls, the familiar facade will stay constant, a piece of medical and architectural history that will last into the 21st century and beyond. ■

*The medical wards in the Bulfinch Building — shown here during the 1920s — were closed in 1977 because of their inability to accommodate newer medical technology. The Inpatient Psychiatry Service, the last inpatient unit in the building, moved to the new Blake Building in spring 1995.*

*(Continued from Page 1)*

Empowered by this new information and real choices, Wyatt became the ultimate decision-maker. Only she could fully appreciate the impact each option might have upon her life, self-image and sense of self-worth. Carlson and Wood pledged to support whatever decision she made.

Wyatt ruled out mastectomy and opted for close follow-up care until menopause, when her risk for developing breast cancer would substantially decrease. Today she is in her mid-50s — healthy, cancer-free, remarried and grateful she was offered a reasonable alternative to radical surgery 10 years earlier.

### *A different approach*

The case underscores the underlying philosophy of Women's Health Associates, formed 10 years ago to practice, study and teach health care as it relates to women.

"Traditionally the subspecialty model of medicine for women was divided into reproductive care and everything else," says Carlson. "We set out to highlight the available services for women at the MGH; provide more comprehensive, less fragmented care; improve access to female physicians, which many women prefer; and fill gaps in the knowledge of how to care for women."

Today approximately 3,600 women's health centers provide care throughout the country. Most offer only gynecological services, and only 10 percent, including Women's Health Associates, provide primary care. The MGH practice has been well received, as evidenced by its steady growth. The service recorded 16,000 patient visits in 1994, and 20,000 visits are expected in 1995. Earlier this year, Women's Health Associates moved into spacious quarters on the 10th floor of the new Blake Building. The current all-female staff consists of 11 general internists, a surgeon, a gynecologist, a psychologist and two nurse practitioners.

"We try to remain true to two guiding principles," Carlson says. "First, we aim to be sure that whatever we as practitioners know about women is translated into the technical domain of women's health. Second, we are consistently advocating and supporting shared decision-making between patient and physician.

"We put the patient in the driver's seat. Once we have provided patients with comprehensive information relevant to their health, the course of treatment is determined cooperatively between the patient and her physician. We try to remain mindful, however, that no matter how strong the relationship with a physician, only the patient can fully understand her world — the medical, social and psychological factors that bring context to her medical treatment."

*Karen Carlson, MD, examines a patient at MGH Women's Health Associates.*

### *Differences between men and women*

An especially compelling case for the study of women's health is found in the different ways in which men and women may experience an illness. Coronary heart disease, for example, is more common in men than in women. The classic model consists of a blockage of the coronary arteries, accompanied by chest pain upon physical exertion, which can be readily diagnosed with a cardiac catheterization and stress test. If the disease worsens, it typically culminates in a heart attack. These patients are generally treated by opening the artery through surgery, angioplasty and/or drugs.

Clinicians and researchers recently observed that women sometimes do not fit this classic model. Such women, typically in their mid-50s, experience chest pain with emotional stress more than with exertion. Neither cardiac catheterization nor stress test is useful in detecting evidence of this type of heart disease, and the patient rarely experiences a heart attack.

In attempting to discover the factors that might contribute to these differences, researchers examined the physiologic differences. They found a different heart disease entity common in women called microvascular angina. Instead of blockages in the major coronary arteries, these women experience spasms in smaller arteries. Because this disease typically does not progress, treatment is directed at relieving the spasms. The role of estrogen in preventing these spasms currently is being studied.

### *Are women "complainers"?*

Female patients commonly have been stereotyped as "complainers." In fact, Carlson points out that research demonstrates the exact opposite. Although women are more likely to recognize and respond to symptoms of non-gender-specific diseases, they are more likely to delay getting care. For example, studies show that women with arthritic joints are less likely than men to report pain. Among patients with normal joints, there is no difference in reporting symptoms. In studies of the common cold, men are more likely than women to overrate their symptoms. Additionally, it has been observed that women ask more questions than men, provide more information and demonstrate more emotion in interactions with medical professionals.

Although surveys still indicate that doctors believe women have more psychosomatic complaints and require more of their time, physicians generally respond positively. In practice, they provide more information to women, more readily engage in partnerships with their female patients, have more conversations and exhibit more empathy in their interactions.

Carlson explains that these tendencies can make a positive contribution to women's health. The amount of information a patient receives can improve compliance, satisfaction, recall of what was discussed and overall health status — trends that lead to more active involvement in the decision-making process.

In an effort to help foster these patient-centered qualities and maximize their impact, Women's Health Associates has established an on-site patient education center. Through a library of books, audiotapes and videotapes, patients can learn more about various issues affecting their own health. These resources can help patients weigh treatment options and make the best possible decision for their own situation.

### *The future of women's health*

The rapid growth of managed care, now permeating the Northeast, poses something of a threat to the women's health model of patient-centered care. At a time when physicians are being challenged to provide health care services more efficiently, today's patients are demanding more from these same providers. The patient's desire for service may run counter to imposed restrictions on care or access to providers.

In the meantime, the topic of debate regarding women's health focuses on who should provide primary care to women: internist or obstetrician/gynecologist. In Carlson's view, all types of providers can get involved in women's care, and she emphasizes the importance of training as many providers as possible to be sensitive to the specific needs of women. The MGH and a number of other teaching hospitals throughout the country are now beginning to offer residencies and fellowships in women's health.

With increased attention on training in women's health, perhaps it will one day be considered a specialty of its own. For now, Carlson has taken the practice of women's health to the next level by co-editing *Primary Care of Women,* along with Stephanie Eisenstat, MD, of Women's Health Associates. More than 60 staff from the MGH and Brigham and Women's Hospital contributed to the effort, one of the first medical textbooks on the subject. ■

# Minaker named to lead new Geriatrics Unit

THE MGH has inaugurated a Geriatrics Unit within the Division of General Medicine in the Medical Service, and Kenneth Minaker, MD, has been named director of the unit. Previously he served as chief of the Geriatric Research, Education and Clinical Center at the Brockton/West Roxbury Veteran's Administration Medical Center, where he also headed the Geriatric Medicine and Extended Care Services.

"Dr. Minaker was the overwhelming choice of everyone we spoke with in our nationwide search to fill this position," says Albert Mulley, MD, director of General Medicine. "He is regarded as perhaps the country's best geriatric clinician and teacher."

While the many services delivered to older patients at the MGH and its community health centers have long been recognized for their excellence, the new unit serves as a hub for primary care geriatric services. The staff — including two additional geriatricians, a geriatric social worker, geriatric nurse practitioner and a gerontologist — provides consultation to other MGH physicians and health care professionals and contributes expertise to research and teaching programs. Four more geriatricians will be added next year.

The unit's first effort is establishing the MGH/Beacon Hill Geriatric Health Practice, a primary care practice opening in September. Minaker explains: "Many older individuals in the Back Bay and on Beacon Hill have expressed a need for easier access to the MGH. We want to reach out to them."

The practice also will expand services at Fox Hill Village, a retirement community in Westwood that is managed and partially owned by the MGH Health Services Corporation, and improve linkages with MGH specialty services. "One of our major goals is working across institutional lines to improve continuity of care," Minaker says. "Collaborative relationships with our colleagues at the MGH, the health centers, Spaulding Rehabilitation Hospital, Fox Hill and with our counterparts at the Brigham and other Partners institutions will make a very complex health system as friendly as possible for our older patients."

### *A focused specialty*

Minaker explains that the focused training and experience the geriatrician brings to the care of older individuals can be essential in dealing with the often complicated medical problems seen in that population. "Geriatricians are devoted exclusively to a single age group, much like pediatricians are devoted to the care of children," he says.

"We understand, as much as anyone does, the process of scenesence [aging], its effects on healthy individuals, how it makes people more susceptible to disease and how it can change the way disease appears. The interaction of scenesence with an illness can create symptoms, such as falling or confusion, not seen in younger individuals. Geriatricians also know how syndromes such as memory loss or frailty interact with other illnesses and may affect how or whether people seek health care. We have to combine the skills of very good internists with some of the expertise of psychiatrists, rehabilitation specialists and other health care providers."

In addition to the medical challenges of caring for older patients, physicians and hospitals today are faced with administrative and financial issues resulting from changes to the federal Medicare system, which provides health insurance to those over 65. For example, many Medicare patients are being encouraged to join managed care plans, in which a single

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## — Geriatrics

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primary care physician coordinates all of a patient's care, often for a set fee. In fact, Partners HealthCare System, the organization overseeing the affiliation of the MGH and Brigham and Women's Hospital (BWH), is developing such a program in collaboration with Blue Cross and Blue Shield of Massachusetts.

Peter Slavin, MD, MGH senior vice president and chief medical officer, notes, "To offer truly coordinated care for those in Medicare managed care programs, we will need the focused expertise that Dr. Minaker and his colleagues bring."

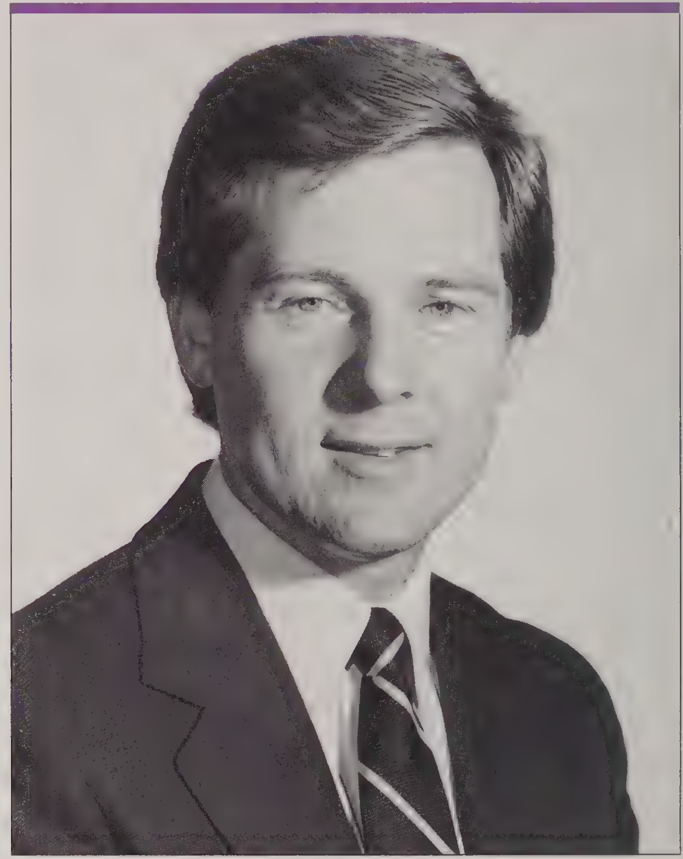
### *Collaboration with BWH and Partners*

Coordination and collaboration are qualities Minaker expects to be hallmarks of his group's relationship with counterparts at BWH and other Partners-affiliated institutions. "Neil Resnick, [MD, chief of the BWH Division of Geriatric Medicine] and I have worked together for 15 years, serving on each others' staffs at the Brigham and the VA, and we have very similar beliefs in quality care, education and scientific rigor," he says.

"Like other services at the two hospitals, ours complement each other. The MGH group is focused on building a fairly large primary care practice, while the Brigham program has more of a subspecialty focus, with specialized treatment and research programs in areas like nutrition, pharmacology and urinary incontinence. We've already started discussing collaborative research projects and blending our educational missions. We've been working together for so long — both at the hospitals and within the Harvard Division on Aging — that we expect to get these programs rolling without skipping a beat."

In his own research, Minaker has investigated how the aging process changes the way certain diseases develop and should be managed. One example is heart failure, a condition in which the heart does not function efficiently, the most frequent problem bringing older patients to the hospital. "Much of the research done in recent years should help us treat more heart failure patients on an outpatient basis, rather than waiting until they have a crisis and must be hospitalized," he explains. "We need to become more sophisticated in predicting who is at risk for heart failure and designing treatment plans that are appropriate for older people, who usually experience more side effects from medication."

Minaker is a graduate of the University of Toronto Medical School and trained in internal medicine at Toronto General and Sunnybrook Medical Centers in Ontario. He held research fellowships in medicine and gerontology at Harvard Medical School and Boston's Beth Israel Hospital, respectively, and a clinical fellowship in medicine at BWH. He has been a member of the staffs at BWH, Beth Israel and the Brockton/West Roxbury VA since 1982 and currently is an associate professor of medicine at Harvard. ■



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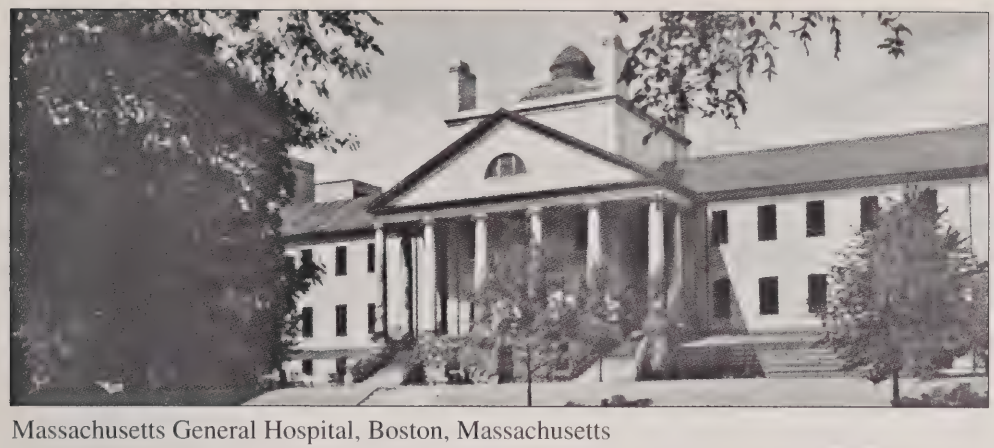


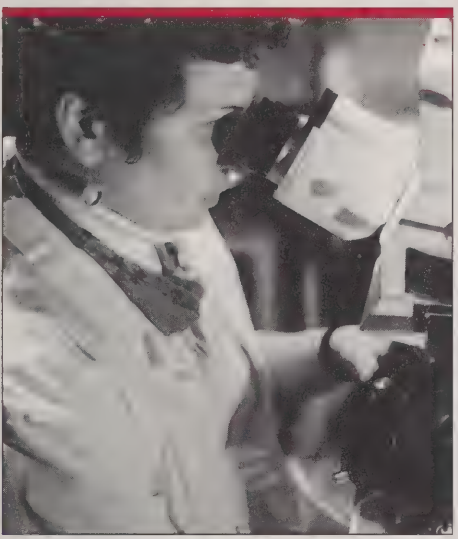
MGH News

Massachusetts General Hospital, Boston, Massachusetts

November / December 1995

**More than skin deep:**

# CBRC investigators explore beneath the surface



*Kristin White, PhD*

As the timer rings, Kristin White, PhD, runs to her lab bench in the MGH/Harvard Cutaneous Biology Research Center (CBRC) to examine a tube of pink liquid — a mixture containing eye cells from the larva of *Drosophila melanogaster*, the household fruit fly. Inside the tube a biochemical reaction identifies cells that are dying — a phenomenon that occurs normally in mammalian tissue development. The experiment's results may illuminate what happens when the natural cell death process goes awry, as in cancer.

His eyes glued to the microscope, Satoshi Amano, PhD, a researcher from Shiseido Company, Ltd., of Japan, examines a slide smeared with cells derived from human foreskin. Working with a team led by Robert E. Burgeson, PhD, associate director of the CBRC, Amano is investigating the complex process of wound healing. He is particularly interested in the critical proteins and molecules that play a role in the adhesion of the outer layer of skin, the epidermis, to the inner layer or dermis.

Caterina Missero, PhD, working with the CBRC group of G. Paolo Dotto, MD, PhD, has been involved in analyzing how and why addition of calcium to a cell culture causes cells from mouse epidermis to differentiate — that is, to produce more specialized cells rather than just reproduce themselves. Because cells in the epidermis normally maintain a fine balance between differentiation and

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# *A new chief takes the reins of MGH Pediatrics*

R. Alan B. Ezekowitz, MBChB, DPhil, used to read the case reports from the Massachusets General Hospital in *The New England Journal of Medicine* while a young medical student in South Africa. "I was bewildered," he remembers, "by the elegance of the logic that was used to derive the diagnoses of those cases. They were wonderful learning tools."

Now Ezekowitz has been named the new chief of the MGH Pediatric Service, succeeding Donald N. Medearis, MD, who had been chief since 1977, the year Ezekowitz earned his MBChB (the equivalent of an MD degree) from the University of Cape Town.

"I am truly honored to be at this great institution," Ezekowitz says, and I am particularly grateful to Dr. Medearis for his support and all he has done for the pediatrics program here."

Ezekowitz' dedication to children has deep roots. Born and raised in Durban, Natal, Republic of South Africa, he remembers being deeply affected by the suffering of children under the repressive rule of the South African apartheid system. "I think the child is the barometer of the family, and the family is often the bellweather of society," he says. "A lot of the impact of social policy gets reflected in the lives of children and their families. That was certainly true in South Africa."

As a medical student, Ezekowitz decided the best way he could help children was to study the basic mechanisms of disease and how such research

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*R. Alan B. Ezekowitz, MBChB, DPhil, examines 9-week-old Anthony Joseph Ligotti as he sleeps in the arms of his mother, Paula.*

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**Gene therapy may work for autoimmune disease**
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# —CBRC investigators explore beneath the skin

*(Continued from Page 1)*

simple growth, understanding what regulates differentiation should be essential for the eventual control of cancer, which results from the uncontrolled growth of cells.

These are experiments within a grand experiment. The CBRC is an enterprise that, in its dynamism, resembles the complex external organ that is its reason for being: the skin.

### *Embodiment of a vision*

Now in its sixth year, the CBRC was born when Shiseido, the Japan-based cosmetics and skin care company, signed an agreement with the MGH and Harvard University to underwrite the establishment of the center. Building on Shiseido's initial 10-year grant of $85 million — which provides an administrative structure, state-of-the-art equipment and a setting conducive to cutting-edge research — CBRC researchers have been able to attract other funding from such sources as the National Institutes of Health. Earlier this year Shiseido extended the grant for an additional five years and $9 million per year.

The grand experiment was largely envisioned by John Parrish, MD, chief of the MGH Dermatology Service and director of the CBRC. "I proposed that collaboration between industry and academia could synergistically bring more results — and faster — than either one going it alone," he says. "Supporting young basic science researchers at the forefront of the new biology and bringing them together with practicing clinicians should produce advances applicable to medicine and health. All the results aren't in yet, but I'm optimistic that the hypothesis will prove to be true."

The CBRC was modeled on Parrish's first brainchild, the Wellman Laboratories of Photomedicine at the MGH. The Wellman Labs, one of the world's first, and possibly the largest, biomedical laser research facilities, gave birth to the MGH Laser Center, now offering innovative treatments for burns, endometriosis, eye diseases and even certain forms of cancer. It was the success of the Wellman that convinced Shiseido of the viability of a similar enterprise dedicated to basic skin biology.

Research agreements with industry such as the collaboration with Shiseido are not unusual for the MGH, explains Ronald W. Lamont-Havers, MD, deputy director for General Affairs at the CBRC. What distinguishes this particular partnership from the others is the level of involvement of both parties. Shiseido researchers participate in CBRC projects, and in the future CBRC researchers will regularly travel to Japan to confer with their counterparts at Shiseido. A video-telecommunication link between the CBRC and Shiseido has been established recently and is now in regular use.

Shinobu Kato, PhD, associate director for Shiseido liaison who also is a visiting scientist at Harvard and the CBRC, explains that the company traces its commitment to health care back 123 years to its founding as Japan's first Western-style pharmacy. For several decades, the company has sponsored international scientific meetings and disseminated research papers on topics such as aging of the skin; biological mechanisms common to the brain, skin, and immune system; and, spurred by concern over the rising incidence of skin cancer, the biology and diseases of pigmentation.

### *Open exchange of ideas, expertise*

At the MGH's modern research building in the Charlestown Navy Yard, the CBRC labs run the length of one side of the third floor. Amidst huge cylinders of nitrogen gas and glass jars brimming with yeast extract, 50 researchers, representing the full spectrum of scientific expertise, freely mix and mingle in the open-design spaces that characterize the Charlestown labs. Cell biologists call questions about a tissue culture to dermatologists; molecular biologists and geneticists cluster in corners to discuss the results of a biochemical analysis; developmental biologists share their thoughts with immunologists in frequently scheduled meetings. A researcher scans the CBRC's own Internet home page, featuring a background that cleverly depicts a pattern resembling a microscopic view of human skin. An easy collegiality exists amidst the serious activity.

"This is a very pleasant atmosphere," says Missero. "The open lab definitely facilitates interaction among the researchers." The CBRC's collaborative spirit assists each researcher's quest to answer a particular question and to add another piece to the jigsaw puzzle of scientific knowledge. Missero — whose work includes studying the cell cycle, the repeated pattern of events leading to the growth and replication of each cell — says: "I find my work really exciting — otherwise I wouldn't be here 10 hours

> **"Supporting young basic science researchers at the forefront of the new biology and bringing them together with practicing clinicians should produce advances applicable to medicine and health.**
>
> **— John Parrish, MD**

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PHOTOGRAPHS: Page 1 (top), 3,7, Susan McGreevey; page 1 (bottom), 6, Arch MacInnes; pages 4,5, Joshua Touster.

every day. The cell cycle, which is the clock of each cell in our body, is fascinating in itself. But it also plays a crucial role in the development of cancer."

### *A short flight from flies to skin ailments*

CBRC research projects run the gamut of topics: from skin aging; to the biology of hair, pigment and skin cells; to skin immunology; to gene regulation. Eventually, many findings made in such "non-human systems" as flies or mice are expected to find their way to commercial, human application. All it takes is a flight of the scientific imagination.

Joseph C. Kvedar, MD, deputy to the CBRC director and a practicing dermatologist, is an advocate for the process of technology transfer. "Whether clinical dermatologists or basic scientists, whether CBRC researchers or Shiseido scientists, we need to use our differences as a source of energy and strength for the endeavor," he says.

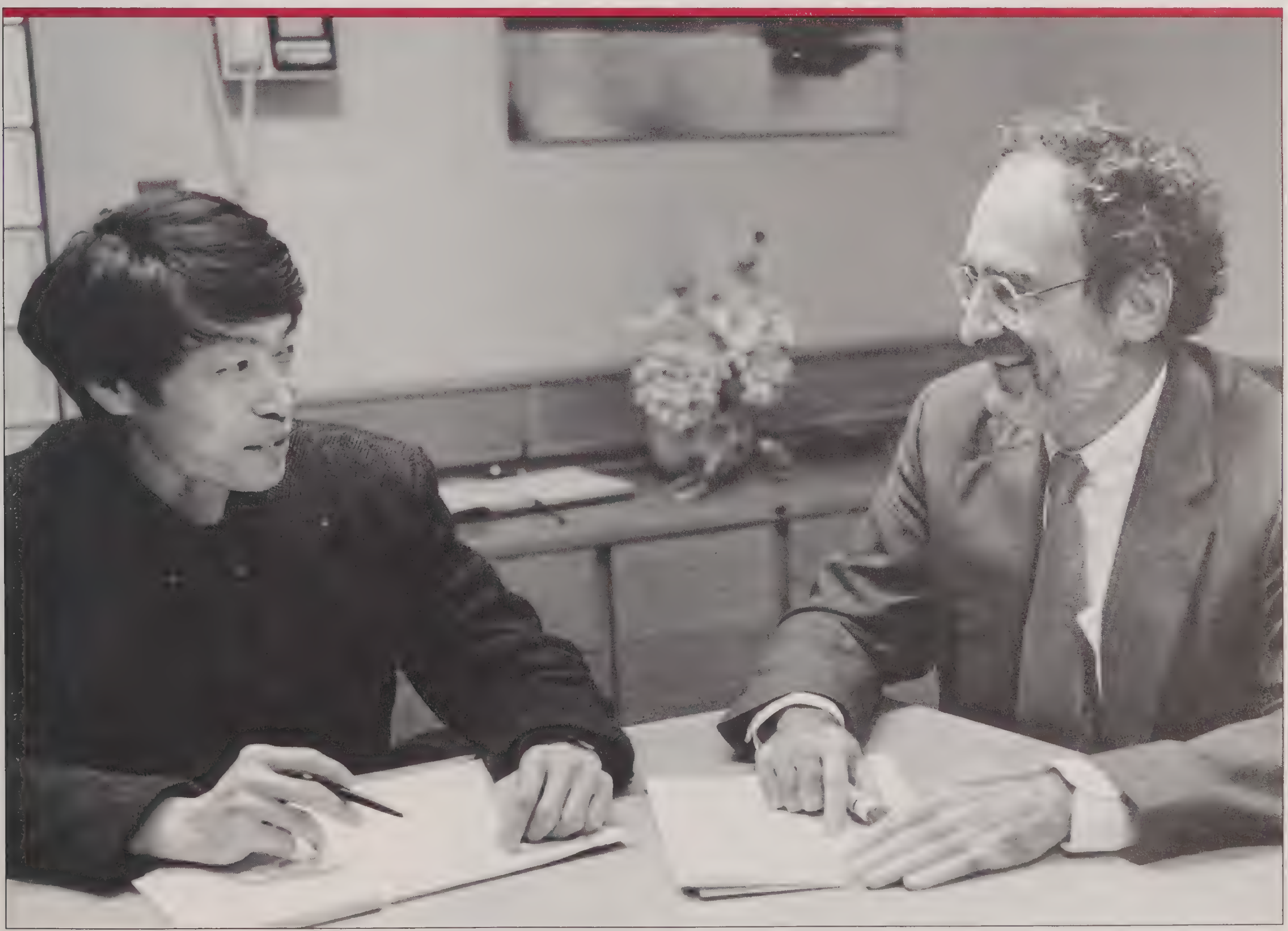
Already, a team led by Ethan A. Lerner, MD, PhD, working with colleagues at several institutions, has learned enough about an insect-derived compound named maxadilan, which relaxes blood vessels in lab animals, that collaborative programs have been established with Shiseido to explore possible clinical applications.

Another group is examining the spontaneous remodeling of skin tissue as it recovers from an injury, while a different team — treating the skin as an extension of the immune system — looks at how Langerhans cells provide specific immunity against skin tumors and the effects that ultraviolet radiation has on these cells.

Clinical dermatologists David Becker, MD, and Bernhard Ortel, MD, divide their time between patient care and skin research and find that one aspect of their work feeds the other. Becker is intrigued by the question of what predisposes some people to develop a common skin cancer, basal cell carcinoma. Ortel, who works at both the CBRC and the Wellman Labs, is inspired by the goal of curing cancer through photodynamic therapy, the use of drugs activated by light, particularly laser light, to destroy malignant tumors.

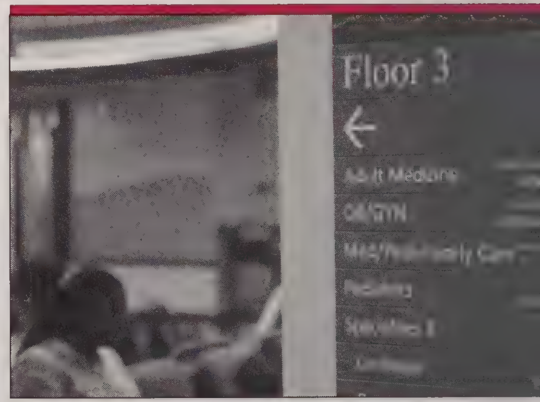
The group led by Burgeson is identifying the molecules that make up the defective basement membrane (separating the deepest layers of skin from adjacent tissues) involved in a painful blistering disease known as epidermolysis bullosa — work that someday may lead to gene therapy for this disease. Another team's explorations of inflammatory skin diseases have implicated certain types of T cells in the degenerative immune system disease lupus and in a rare but serious skin disorder called lichen planus.

Picking up her briefcase to head home from the CBRC, White can't resist one last look at the mixtures in her test tubes. Then she switches off the light and walks out the door. Meanwhile, in the darkened lab, fruit flies buzz in glass jars; centrifuges shake, rattle and whirl; and skin cells multiply in laboratory dishes. And medical science progresses. ■



*Shinobu Kato, PhD, associate director for Shiseido liaison, discusses joint research projects with John Parrish, MD, director of the CBRC.*

MGH
Revere
HealthCare Center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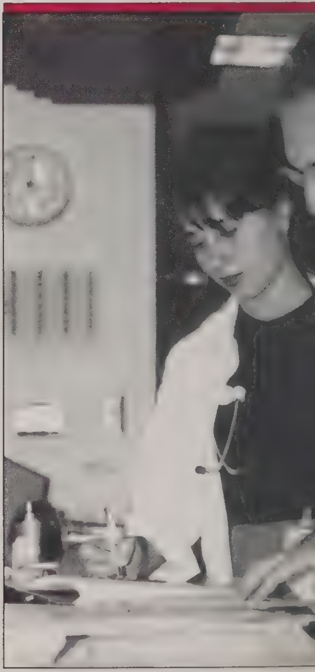
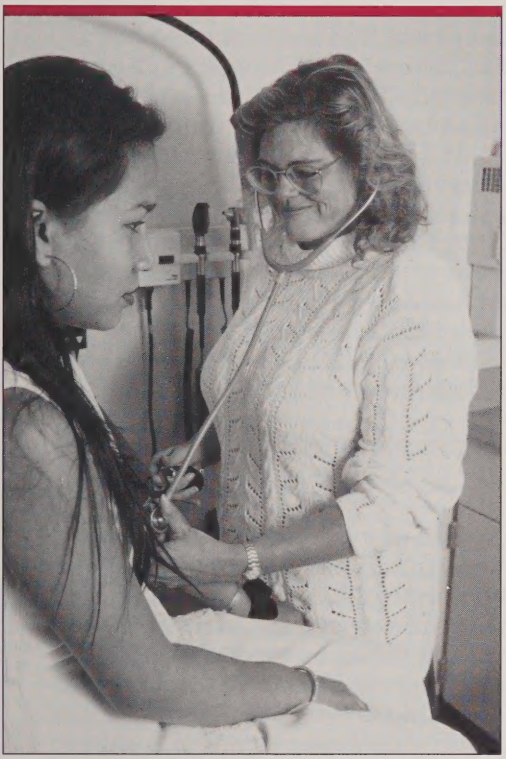


# Health care comes to the beach



***Clockwise from top:*** *Kim Meehan, RN, ANP, examines Sophea Chea.*

*Roger Pasinski, MD, (center) with asthma patient Roeun Yim (left) and Sonantea Ouk, one of the four Cambodian interpreters on staff at the health center.*

*Christopher Zimmerman, MD, Internal Medicine-Pediatrics, confers with Gina Marano, CPA, about the day's patient visits.*

OCEAN AVENUE in Revere was once teeming with young people who, on hot summer days and nights, lined up to enjoy the amusement park attractions across from the beach. Today the roller coaster and other attractions are but a memory, and those young people are now parents and grandparents. But many are still returning to the site of the old amusement park.

The MGH HealthCare Center • Revere, a staple of primary health care for residents of Revere and its surrounding communities since 1981, recently relocated to a new facility at 300 Ocean Ave. And somewhat like the amusement park before it, this neighborhood health center has become one of the ties that bind the residents of this seaside community together.

The move to the new location reiterates the health center's long-term commitment to the people of the community. Operating for many years in a small space at the Revere Post Office building, the center had outgrown the cramped quarters. The new state-of-the-art facility has five times the space of the old location, allowing the center to offer more specialized care to complement existing primary care services.

"This current location gives us the opportunity to meet practically all of our patients' health care needs in one facility right in their neighborhood," says Roger Pasinski, MD, medical director of the center. "Traditionally, if we did not offer a service at the health center, we would refer patients to the MGH. Because many of our patients have been coming to the health center for years, however, it seemed important to strengthen their relationships with their current caregivers. We wanted to be able to offer them most of the services they needed right here." These newly available services — which include laboratory and mammography services as well cardiac rehabilitation, and physical and occupational therapy — will enhance the obstetrical, dermatological and medical services already offered.

The patient population at Revere is as diverse as the services offered, and it is not unusual to hear conversations in Spanish and Khmer in the halls of the health center. Many staff members are bilingual and are able to provide translation services for their Hispanic and Cambodian patients. In addition, the staff is keenly aware of cultural differences and can extend personal support to those not yet acclimated to American culture. Even the signage throughout the center appears in multiple languages, a small but significant detail that reflects the center's commitment to its community.

This commitment goes both ways. More than 2,000 patients and friends of the health center celebrated with the staff at the dedication of its new home this summer.

"Our patients have stuck by us for a long time," says Pasinski. "The dedication and open house were just a small way of thanking them for their continued support over the many years we have been in Revere. We will continue to provide the care and support that our patients need, and we hope that they will continue to let us know how we can meet all their medical needs." ■

## —New chief of Pediatrics

*(Continued from Page 1)*

could be applied clinically. Research continues to be a major part of his career.

"The exciting part of biology is that we've probably learned more in the last five years than we've learned in the last 2,000. And a lot of those discoveries are having an impact on the treatment of children," he says.

Ezekowitz currently is working on a collaborative study with colleagues from the Yale Medical School, France, Japan and Germany. The project will examine the primitive immune systems of insects in the hopes of discovering a molecular secret that could be applied to fighting infections in infants. For instance, notes Ezekowitz, flies live in filth but, through some unknown biological mechanism, they resist infection.

Given the importance of research in his career, it is not surprising that Ezekowitz is also concerned about current trends in research funding. According to Ezekowitz, one way pediatricians must serve as advocates for children is by making sure that bench research is applied wherever possible at the bedside. "It's a little ironic," he notes, "that the efforts in the political arena to restrict public funds for research are now threatening to obstruct the ability of physicians to apply what has been learned in basic science to the delivery of care to patients."

After serving an internship and residency in a South African hospital, Ezekowitz journeyed to Great Britain where he worked part time as a pediatrician while earning the equivalent of a PhD at Oxford University. A year of postdoctoral research at Oxford followed, and then Ezekowitz set sail for Boston, where he joined the staff of Children's Hospital in 1984 and became director of the Children's Hospital General Clinical Research Center in 1991.

Kurt Isselbacher, MD, director of the MGH Cancer Center, led the search committee that selected Ezekowitz for his new position.

"Dr. Ezekowitz emerged at the top of a group of outstanding national candidates, and our committee unanimously concluded that he was the ideal person to lead MGH Pediatrics into the next century," Isselbacher says.

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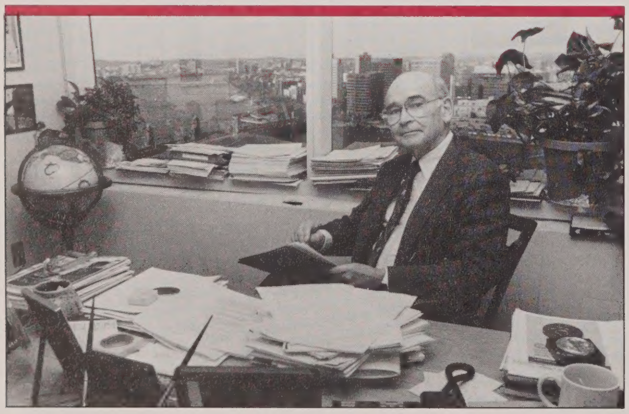
# Looking back over 18 years of service

FROM HIS TINY OFFICE on Ellison 19, Donald N. Medearis Jr., MD, has a spectacular view over the Charles River to the west of Boston. He also enjoys an insider's view of the last 18 years of pediatric medicine at the MGH, the time he served as chief of the hospital's Children's Service.



*Donald N. Medearis Jr., MD*

Recalling the major milestones during his tenure, Medearis gestures toward the window: "For one thing, the facilities here have been almost completely rebuilt. When I came in 1977 the service was in the old Burnham and Clinics buildings; now we're in the new Ellison Building."

A very important part of the growth and development of the service was the advent of the Obstetrics Service in 1994, Medearis says. "Having pediatrics linked with obstetrics allows us to do a lot more in education, care and research."

"Moreover," Medearis notes, "with OB we can offer care to the entire family; that is very much the intent and philosophy of the Partners HealthCare System."

"I think that was an important element in the hospital's decision to take on the responsibilities and burdens of an obstetrics service. It's a great benefit not only to pediatrics but to the hospital, as well as to the patients we serve."

The establishment of an integrated medicine and pediatrics residency program at the MGH in 1990 is another milestone on Medearis' list because it also supports family-focused care by providing education and training for physicians who will care for patients of all ages.

Medearis has seen many changes in the care and treatment of children in his 37 years in academic pediatrics. The development of respiratory support mechanisms and the new drugs used in the care of premature infants have been remarkable strides in care, he says.

Citing the survival today of a high percentage of children with acute lymphatic leukemia, a disease once almost uniformly fatal, he points to the advent of chemotherapy as another striking development. Even closer to his heart, since he has long been involved in research on viruses, is the development and widespread use of vaccines for polio, measles and other childhood infections.

Now, in Medearis's view, pediatric medicine must redouble efforts to address medical problems that stem from socioeconomic factors. "We have eliminated some of the scourges of infectious disease, but what we have left are congenital anomalies that we can't prevent; the horrible accident; suicide and homicide rates in adolescents; and pyschosocial problems that have to do with abuse, neglect and deprivation," he notes.

But as Medearis looks to the future, he also will be looking to the past. Lining almost one entire wall of his office are 90 volumes of the medical records of the early years of the Children's Service, from 1910 to 1922. These volumes will be the focus of a study that Medearis hopes will one day become a book. "I'd like to analyze the data in light of the social and political context of the times and contrast it with the present," he says. Medearis also will continue to teach and consult at the hospital.

"The MGH is a wonderful place," Medearis says, "and I think that the Children's Service is very strong and will continue to do very well under the leadership of Dr. Ezekowitz. It's been a real privilege to serve the MGH with my colleagues on this service." ■

"With all the new developments and changes in health care," adds Medearis, "I think it is a very propitious time for a transition to new leadership — leadership that can continue for the next decade and beyond. I think MGH Pediatrics is going to become an ever more important component of the Partners system."

Samuel O. Thier, MD, president of The Massachusetts General Hospital and Partners HealthCare System, agrees. "The MGH Pediatric Service plays a central role in the Partners system. Dr. Ezekowitz brings great intelligence, experience and concern for children and their families. He will help us continue to focus on providing the highest quality care to our youngest patients."

Ezekowitz aspires to an even greater role for MGH Pediatrics, to develop a national model for providing care to children in a way that can adapt to the rapidly changing health care delivery environment and the difficulty of maintaining quality care and simultaneously cutting costs.

"We have to be aware of our community," he notes, "not only our colleagues but most important our patients. We must always recognize that our ultimate constituent and our top priority is the health and welfare of children and adolescents." ■

# MGH/BWH team: gene therapy may work for autoimmune disease

AUTOIMMUNE DISORDERS like multiple sclerosis, rheumatoid arthritis and Type 1 diabetes involve a mistaken attack on the body's own tissues by cells of the immune system. Now a team of scientists from the MGH and Brigham and Women's Hospital (BWH) has demonstrated, for the first time, the possibility of treating autoimmune disorders with gene therapy. By inserting normal copies of genes that may contribute to development of Type 1 diabetes into immune cells from diabetic patients, the researchers corrected an abnormality in a molecule involved in "educating" the immune system not to attack the body's cells.

Denise Faustman, MD, PhD, of the MGH Diabetes Unit says, "Our study shows that someday we might be able to correct a diabetes-associated defect in a patient's own cells and reinfuse the cells into the patient, keeping high-risk individuals from developing Type 1 diabetes or preventing recurrence in patients who have had a pancreas transplant."

Fred Wang, MD, of the BWH Department of Medicine, adds: "This was a complex, technically difficult study that we were able to accomplish by bringing together two state-of-the-art laboratories. It adds another piece to the very complicated puzzle of Type 1 diabetes." Faustman and Wang were co-leaders of the research project.

Type 1 diabetes develops when the insulin-producing beta cells of the pancreas are destroyed. Normally, the immune system components called killer T cells learn whether they should attack entities they encounter through the action of special molecules, called MHC Class I and II, which sit on the surface of immune system components called B cells and macrophages. MHC Class II teaches T cells to recognize proteins from invading microorganisms, while MHC Class I displays tiny bits of "self" proteins from the body's own tissues, which T cells should leave alone *(see sidebar, Page 8).*

In 1991, Faustman's research team discovered that macrophages from children at high risk for diabetes had unusually low levels of MHC Class I molecules on their surfaces, an observation that helped to clarify Class I's role in teaching T cells to recognize self proteins. The finding was controversial, however, because decades of genetic studies strongly suggested that Type 1 diabetes was associated with a genetic abnormality on the region of chromosome 6 responsible for the Class II molecules. Faustman theorized that the problem was not with the Class I molecules themselves but with proteins involved in transporting the molecules to the cell surface, proteins coded in the section of chromosome 6 that also controlled Class II expression.

The current laboratory study looked at two of those transport proteins, called Tap-1 and Tap-2. Faustman's team wanted to see what would happen when they inserted normal genes for these proteins into B cells from diabetic patients. Attempts using standard gene therapy techniques failed to produce cells that consistently produced the normal transport proteins. Then Wang and his colleagues brought to the effort their expertise in systems that use viruses to transfer genes into cells. Wang's group developed a system that successfully used the Epstein Barr virus, which causes mononucleosis, to insert functional Tap genes from nondiabetic patients into B cells from diabetic patients.

*(Continued on Page 8)*

*Denise Faustman, MD, PhD, and Fred Wang, MD, examine test results indicating the levels of an important molecule on the surface of immune system cells.*

(Continued from Page 7)

Cells from 40 percent of diabetic patients responded to normal Tap-1 genes by showing normal levels of Class I molecules on their surfaces. Cells from another 40 percent of patients similarly responded to normal Tap-2 genes. Cells from nondiabetic patients that received the same Tap genes showed no change in the number of Class I molecules, implying that the procedure corrected a defect rather than just indiscriminately increasing the presence of Class I molecules.

Although this study strongly suggests that problems with Tap-1 and Tap-2 genes may cause at least some cases of Type 1 diabetes, no one has proven that these genes are mutated in patients with the disease. In fact, the researchers suspect that the genetic basis of diabetes may be much more complicated than a problem with a single gene.

"We think that people who develop Type 1 diabetes don't necessarily have defective genes," Faustman says, "but that normal variations of key genes in this very important region of chromosome 6 are incompatible with the variations of other genes in the same area. It's like the engine of a car. If you try to put Ford parts into a Volkswagen engine, they won't work. The parts are perfectly fine, but they aren't intended to work in that particular engine."

Before any human tests of this approach can be carried out, scientists must better define what goes wrong in the immune system cells of diabetic patients and develop improved ways to monitor whether higher levels of MHC molecules on cell surfaces result in better T cell education. A crucial requirement will be developing safer gene therapy transfer methods.

"The vectors currently used in gene therapy trials are not able to cause illness," Wang says. "But the virus we used in this study can cause disease. Before we can apply these *in vitro* results in patients, we need to eliminate the risk of infection by finding newer, more creative approaches to gene therapy." ■

## The education of the immune system

THE BODY's system for fighting off infection is like an army, with specialized "soldiers," the immune system cells, that have specific roles to play. Some cells directly destroy invading bacteria or viruses as soon as they are encountered. Others act as advance scouts, traveling throughout the body on the lookout for invaders. When they encounter an "enemy," they carry key information back to other cells that, in turn, produce antibodies uniquely designed to recognize disease-causing organisms and mark them for destruction.

The key immune components called killer T cells go through a special process of education before they embark on their task. Not only must they recognize invading microorganisms that are to be destroyed, they also must recognize the tissues of the body, which are to be left alone. The process by which T cells are educated is only beginning to be understood. But current knowledge, some of which was developed at the MGH, indicates that two varieties of MHC (major histocompatibility complex) molecules make the difference between whether T cells learn to ignore or destroy particular tissues.

MHC molecules sit on the surface of immune cells called B cells and macrophages. These cells have specialized immune system roles of producing antibodies or engulfing invaders, respectively, but in addition both types of cells chop up bits of protein they have ingested and display them on their surfaces via the MHC molecules. Proteins from viruses or other disease-associated organisms are displayed on MHC class II molecules, and the MHC class I molecules hold bits of "self" protein from the body's own cells.

Somehow the killer T cells learn that cells and tissues with proteins displayed on Class II molecules should be destroyed while proteins displayed on Class I molecules should be left alone. But sometimes the process goes wrong, and the T cells don't get the message that particular proteins should be protected. When that happens killer T cells can attack the body's tissues, resulting in autoimmune disease. ■

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